For Clinical Neurology, 3d edition,

by A. B. Baker (ed.), Hoeber, New York

Chapter 27

DISORDERS OF THE HYPOTHALAMUS AND PITUITARY GLAND

Webb Haymaker and Evelyn Anderson

Webb Haymaker, M.D.

National Aeronautics and Space Administration

Ames Research Center, Moffett Field, California

Evelyn Anderson, Ph.D., M.D.

National Aeronautics and Space Administration

Ames Research Center, Moffett Field, California

DISORDERS OF THE HYPOTHALAMUS AND PITUITARY GLAND

CHAPTER 27

Disorders of the Hypothalamus and Pituitary Gland

WEBB HAYMAKER and EVELYN ANDERSON

The hypothalamus has a sphere of influence of astonishing proportions. It contains specific neuronal assemblies concerned in survival and propagation of the species. It is largely responsible for the rhythmicity of bodily functions and it serves to stabilize the milieu intérieur in the face of any stressful situation. It possesses mechanisms essential for the regulation of food intake and energy expenditure and for the maintenance of water ~~and~~ balance & and salt balance. In warm blooded animals the hypothalamus serves to keep the body temperature within certain prescribed limits. Sleep and wakefulness are in its province. Without its influence there would be no means for the expression of emotional behavior. Moreover, the hypothalamus contains mechanisms that pattern the motor accompaniments of all these activities.

The hypothalamus contains a multitude of receptor mechanisms excitable both by neural and hormonal means. These are presided over by the limbic lobe, that phylogenetically old part of the brain from which the neocerebrum subsequently mushrooms. Not only that, but its neuron assemblages interact with those of other forebrain fields and with the reticular substance of the midbrain through reciprocating circuits. Among hypothalamic effector mechanisms are neurosecretory neurons through which the functioning of the neurohypophysis and adenohypophysis are controlled.

The description of the hypothalamus that follows will no doubt give the impression that the hypothalamus is a well defined, sharply delimited part of the brain, an isolated island unto itself, so to speak. However, anteriorly and posteriorly the hypothalamus is contiguous with gray matter from which it can be delineated only with difficulty, and with interlinking fiber pathways.

ANATOMY OF THE HYPOTHALAMUS

The hypothalamus borders the inferior half of the third ventricle and is separated from the thalamus by the hypothalamic sulcus. Anteriorly the hypothalamus extends to the lamina terminalis. Posteriorly it is bounded by an imaginary plane extending from the posterior commissure dorsally to the caudal aspect of mamillary bodies ventrally. Bordering its lateral aspect is the internal capsule and the upper extension of basis pedunculi rostrally and the subthalamus caudally.

The hypothalamus is divisible into a medial portion and a lateral portion. The tuber cinereum, posttuberal region, and mamillary bodies make up the medial portion, and the lateral preoptic-lateral hypothalamic area the lateral. The "tuber cinereum," a term referring to the domed protrusion from the basal surface of the hypothalamus, lies between the more rostral part of the optic tracts. Issuing from it just behind the optic chiasm is the infundibulum of the neurohypophysis. The hypothalamic substance bounded basally by the tuber cinereum is called the "tuberal region." Being ill-defined, the number of nuclei included in this region varies considerably with the author; ordinarily included are the tuberoinfundibular (or infundibular) and ventromedial nuclei; other nuclei commonly included in the tuberal region are indicated in Table 27-2. Behind the tuber cinereum and in front of the mamillary bodies is the "posttuberal region," which consists of a narrow isthmus of tissue which projects from base of the hypothalamus as the postinfundibular eminence. The lateral preoptic area and the lateral hypothalamic area are contiguous. The main surface landmarks of the lateral hypothalamic area are two or three tiny rounded bodies, the nuclei tuberis laterales.

Derivation of the Hypothalamus and Hypophysis

Concepts as to the derivation of the hypothalamus date back to His, Johnston,

Fig. 27-1

and Streeter (Fig. 27-1a). According to them the sulcus limitans of the midbrain extends forward as the sulcus diencephalicus ventralis (hypothalamic sulcus in the adult) to terminate in the optic, or preoptic, recess; the basal plate is continuous forward as the hypothalamus, and the alar plate as the thalamus and epithalamus and the telencephalon.

Another concept - of Kingsbury, Schulte and Tilney, and Kuhlenbeck - originated from the identification of four longitudinal diencephalic zones: epithalamus, dorsal thalamus, ventral thalamus, and hypothalamus, with their boundaries represented by three sulci in the wall of the third ventricle.[106,263,308,309,327,328] Inherent in this scheme (Figs. 27-1a and

Fig. 27-2

Fig. 27-2) is the view that the sulcus limitans of the neural tube ends in the rostral midbrain, in the region of the mamillary recess. The basal plate of the midbrain would thus have its rostral end in the mamillary recess, while the alar plate would extend forward and include all the diencephalon as well as the telencephalon. The preoptic region, previously regarded as a telencephalic component (telencephalon impar), was shown to originate from a hypothalamic anlage.[106,325,327] From the caudal dorsolateral part of the tuberomamillary anlage arose the subthalamic nucleus, which migrated to become a component part of the subthalamus. The rostral dorsolateral part of this anlage gave rise to the entopeduncular nucleus, which ultimately became the globus pallidus. The embryonic ventral thalamus formed the zona incerta (a component of the subthalamus) and the reticular nucleus of the thalamus.[326] Thus, according to this scheme the subthalamus is derived from hypothalamic and ventral thalamic anlagen.

The two concepts already dealt with were based on studies of many vertebrates, including man. A more recent view -- that by Spatz, Kahle, and Richter -- is based solely on a study of human embryological material (Fig. 27-1c). It holds that the subthalamus is derived from a separate diencephalic anlage,

situated between the hypothalamic and ventral thalamic anlagen, and that it continues forward from the midbrain tegmentum (or basal plate into the diencephalon).[297,298] According to this view the sulcus limitans extends rostrally to the sulcus of the interventricular foramen (of Monro). The subdivisions proposed, from dorsal to ventral, are given in Table 27-1. Inclusion of subthalamus as a fifth diencephalic longitudinal zone was based largely on time difference in maturation of different components of the diencephalic matrix (situated along the wall of the third ventricle), the matrix of the subthalamic anlage undergoing early "exhaustion." The derivatives of the subthalamic anlage, according to this view, were the subthalamic nucleus, the entopeduncular nucleus, and the globus pallidus. The zona incerta and reticular nucleus of the thalamus arose from the embryonic ventral thalamus. In the course of development the entopeduncular nucleus became the internal segment of the globus pallidus. The external segment of the globus pallidus had its anlage somewhat more rostrally in the subthalamic anlage and directly behind the lower limit of the telo-diencephalic fissure. During the fifth month the subthalamic derivatives turned from the sagittal to the coronal plane, whereby the subthalamic nucleus lay medially and the internal and external segments of the globus pallidus laterally. This rotation was contingent on the elongation of the striatum in the caudal direction.[459,516] In how far this proposed scheme applies to subhuman species still needs to be ascertained.

Table 27-1

Fig. 27-3

At an early embryonic stage, the hypophysis begins to take form (Fig. 27-3). A diverticulum from the embryonic buccal cavity grows dorsalward to become adherent to the base of the forebrain. This diverticulum is known as Rathke's pouch, and its region of attachment to the buccal cavity, the craniopharyngeal duct. The wall of the diverticulum becomes the adenohypophysis, and its cavity the interglandular (or Rathke's) cleft. Rathke's pouch rapidly enlarges to form an irregular sac, and flattened against it is a downgrowth of tissue from

the floor of the third ventricle, which is to become the neurohypophysis. At the end of the second month, when the craniopharyngeal duct has become a cord, Rathke's pouch is no longer connected with the buccal epithelium. Thus, what was formerly an open pouch is now a closed epithelial sac, which is cupped or invaginated to receive the neural tissue that is to differentiate into the neurohypophysis. Remnants of the craniopharyngeal duct frequently persist in the pars intermedia, posterior lobe and basisphenoid, and residual squamous and other types of epithelial cells are often found within the hypophysial stalk, particularly at its upper and lower ends.[67,489] A pharyngeal hypophysis (Fig. 27-3) is practically always to be found; it tends to increase in size during the first few months of neonatal life. It may become as large as 6.62 X 1.5 X 0.35 mm. Chromophobe cells in the pharyngeal hypophysis are very few (approximately 1.0 per cent), and chromophils still fewer; the majority are undifferentiated epithelial cells.[379]

Classification of the Hypothalamic Nuclei

The hypothalamus may be subdivided in various ways.[106,402] Three longitudinal hypothalamic zones may be distinguished: a lateral, a medial, and a periventricular zone.[121] This classification is consistent with the primitive organization found in all vertebrate forms below the reptiles. In these forms the lateral zone is almost acellular and is traversed by a robust longitudinal fiber system, the medial forebrain bundle. In higher forms this zone becomes occupied by multiform nerve cells, the lateral preoptic and lateral hypothalamic nuclei. During phylogenetic development the medial zone lacks a prominent longitudinal fiber system. However, it undergoes progressive differentiation into a relatively homogenous medial component, the periventricular zone, and a more differentiated outer region, the medial hypothalamic zone, which contains numerous nuclei. In the human brain a separation of the medial zone into periventricular and medial hypothalamic zones is not as well defined as in

lower forms.

The hypothalamic nuclei may also be classified on the basis of degree of myelination: the medial tuberal nuclei are myelin-poor, while the nuclei of the lateral preoptic-lateral hypothalamic area and the mamillary body contain abundant myelinated fibers.

A further classification, the one adopted in the present chapter (Table 27-2), is in terms of regions of the hypothalamus, from rostral to caudal.[463]

Table 27-2

Periventricular Region

The preoptic periventricular nucleus surrounds the wall of the rostral end of the third ventricle in the region of the preoptic recess and stands in close relation with the suprachiasmatic nucleus and the nucleus supraopticus diffusus. Its cells intermingle with cells of the subependymal matrix.

The posterior periventricular nucleus borders the lower aspect of the caudal end of the third ventricle.

Preoptic Region

The preoptic region of the hypothalamus is bounded rostrally by the lamina terminalis and caudally by an imaginary plane situated 5 or 6 mm. behind the lamina terminalis. Within it are two cell aggregates, the medial and the lateral preoptic nuclei (Figs. 27-4 and 27-5), the borders of which are poorly defined microscopically. The cells of these two nuclei are small.

Figs. 27-4 27-5

Supraoptic or Rostral Region

The nucleus supraopticus diffusus is situated along the caudal border of the optic chiasm. Its cells, which are small, are intermixed with fibers of the dorsal supraoptic decussation.

The suprachiasmatic nucleus, as its name implies, lies immediately above the optic chiasm. It borders the lowermost part of the third ventricle.

The anterior hypothalamic nucleus constitutes another cell aggregate in

the rostral hypothalamic region. It is located between the medial preoptic nucleus rostrally and the ventromedial and dorsomedial nuclei caudally. Moreover, it lies dorsolateral to the suprachiasmatic nucleus and ventral and rostral to the more inferior part of the paraventricular nucleus.

The supraoptic nucleus consists of three separate components named in accordance with their orientation to the optic tract: dorsolateral, dorsomedial, and ventromedial. Separation of the nucleus into these components is dependent on expansion of the optic tract during development. The nucleus extends along the upper surface of the optic tract from the level of the optic chiasm to the rostral border of the nuclei tuberis laterales (Figs. 27-4 and 27-5). Its cells are large, of uniform appearance, and closely aggregated. Scattered in the region between the supraoptic and paraventricular nuclei are clusters of cells called accessory supraoptic nuclei. They have the same characteristics as the cells of the supraoptic nucleus proper.

The supraoptic nucleus is the chief source of the fibers extending into the neurohypophysis. It seems likely that the nucleus receives short fibers from the dorsally adjacent lateral hypothalamic nucleus as well as from the nucleus of the diagonal band of Broca, which extends along its lateral side.

The paraventricular nucleus consists of a thin aggregate of cells located close to the third ventricle in the more dorsal party of the hypothalamus (Figs. 27-4 and 27-5). Above it is the dorsal hypothalamic nucleus. Unlike the supraoptic nucleus, the paraventricular nucleus is composed of nerve cells of varied size. The nucleus receives nerve fibers from the periventricular fiber system. Other afferents to the nucleus appear to arise in the lateral hypothalamic region, and it is likely that the paraventricular nucleus also receives fibers from the subthalamic region. Efferent fibers from the larger paraventricular cells pass downward (as the tractus paraventricularis cinereus) to reach the supraoptic nucleus. Some fibers may synapse in this nucleus, but

most continue downward in the supraopticohypophysial tract to terminate in the neurohypophysis. The medium-sized and small cells in the paraventricular nucleus are believed to form a tract that passes caudally into the more medial part of the midbrain.

Both the supraoptic and paraventricular nuclei have an extraordinary capillary richness, the former containing 2600 capillaries per cubic millimeter of tissue and the latter about half that number, whereas elsewhere in the brain the capillary count is usually below 1000.[189] A peculiarity of the vascular system in these two nuclei is that, like the neurohypophysis and unlike other hypothalamic nuclei, the vessels are surrounded by argyrophilic connective tissue fibers.

Tuberal or Middle Region

The tuberoinfundibular nucleus is also called the infundibular nucleus[103,104,519] and the nucleus periventricularis arcuatus[463] (or simply the arcuate nucleus). Many of its cells together with a few cells of the ventromedial nucleus are situated in the infundibulum (or median eminence) of the neurohypophysis. The tuberoinfundibular nucleus is bounded dorsally by the ventromedial nucleus; ventrally it spreads out beneath the third ventricle, where (as stated) some of its cells merge with the infundibulum. The tuberoinfundibular is the only nucleus not separated from the third ventricle by subependymal matrix. The tuberoinfundibular nucleus is generally described as extending caudally in diminishing mass to the region of the premamillary nucleus.[104] However, it has been contended[495] that what is ordinarily called the tuberoinfundibular nucleus is, in actuality, two nuclei, the cells of which exhibit differing reactions under pathological conditions: the subventricular nucleus, located mainly in the postinfundibular eminence and composed of cells of varied size, and the posteromedial tuberal nucleus, extending to the cleft between the mamillary bodies and composed of large cells. The fibers of what we

shall call the tuberoinfundibular nucleus are delicate and nonmyelinated; they extend into the infundibulum, where they end about capillary loops and other capillary formations. This group of fibers constitutes a neural part of the neurovascular link between the hypothalamus and anterior lobe of the pituitary.

The ventromedial nucleus is a relatively large cell mass occupying the tuberal region (Figs. 27-4 and 27-5). It is bounded inferiorly by the tuberoinfundibular nucleus, while caudally some of its cells mingle with cells of the premamillary nucleus. Abundant interconnections exist between the ventromedial nucleus (and other medially situated nuclei) and cells of the lateral hypothalamic area.[540] Moreover, the ventromedial nucleus is connected with the amygdala and orbitofrontal cortex via relays in the lateral preoptic and rostral hypothalamic regions. Efferent fibers from the ventromedial nucleus pursue a course down the brain stem in the periventricular and lateral hypothalamic (autonomic) systems. Some fibers may extend into the infundibulum as components of the tuberohypophysial tract.

The dorsomedial nucleus surmounts the ventromedial nucleus and extends dorsally to a short distance beneath the hypothalamic sulcus. Rostrally this nucleus together with the upper part of the ventromedial nucleus lies next to the anterior hypothalamic nucleus. The dorsomedial nucleus seems to have developmental and functional connections with ventral thalamic structures, e.g., the reticular nucleus of the thalamus and the zona incerta.

The dorsal hypothalamic nucleus is rather poorly defined (Fig. 27-5). It occupies a position superior to the dorsomedial nucleus and a short distance inferior to the thalamus, and it lies rostral to the posterior hypothalamic nucleus. Lying lateral to the dorsal hypothalamic nucleus is the zona incerta.

Posttuberal Region

The posttuberal region is occupied by the posterior hypothalamic nucleus. This cell aggregate lies between the ventromedial and dorsomedial nuclei rostrally

and the mamillary complex caudally, though some of its cells are situated dorsal to the mamillary body where they are contiguous with cells of the central gray substance of the midbrain. Medially the nucleus borders the ependymal matrix of the third ventricle.

Mamillary Region

The medial mamillary nucleus comprises the major part of the mamillary body (Fig. 27-5). Its medial subdivision, composed of medium-sized cells, gives rise to most of the mamillothalamic tract; its lateral subdivision, made up of small cells, receives most of the fornix.[244,466] The most prominent efferent pathways are the mamillothalamic and mamillotegmental tracts, the former terminating in the anterior thalamic nuclei, and the latter in the mesencephalic dorsal and ventral tegmental nuclei of Gudden.

Bordering the mamillary body are a number of small nuclei, as follows: The lateral mamillary nucleus consists of a narrow band of fairly large cells located next to the ventrolateral edge of the medial mamillary nucleus (Fig. 27-5). This lateral nucleus is part of an ancient system antedating, phylogenetically, the mamillary bodies.[244,466] Afferent fibers to this nucleus are received by way of the mamillary peduncle from mesencephalic tegmental nuclei. Many collaterals pass from the mamillary peduncle into the medial mamillary nucleus and to more rostral parts of the hypothalamus. The nucleus intercalatus consists of a small group of large, polygonal cells situated dorsal to the lateral mamillary nucleus and lateral to the more rostral part of the medial mamillary nucleus.[82,463] The premamillary nucleus hugs the rostral border of the medial mamillary nucleus. It lies caudal to the ventromedial nucleus and ventral to the bulk of the posterior nucleus. The supramamillary nucleus is fairly discrete and surmounts the more caudal part of the medial mamillary nucleus in the region of the mamillothalamic tract. The nucleus is composed of small isomorphous cells. Synonyms are: intercalated nucleus of the supramamillary decussation[120] and medial postmamillary

nucleus.[82]

Lateral Region

The lateral hypothalamic area, which contains mostly small cells, extends throughout the lateral hypothalamic region. Medially it is limited by the mamillothalamic tract and the anterior column of the fornix. Rostrally it is continuous with the lateral preoptic nucleus, while caudally it merges with the mesencephalic ventral tegmental area of Tsai (Figs. 27-7 and 27-8). This cell aggregate, also known as the nucleus of the mamillary peduncle, is situated ventral to the red nucleus and forms the most direct caudal continuation of the lateral hypothalamic area.

The tuberomamillary nucleus occupies the more caudal part of the lateral hypothalamic area (Figs. 27-4 and 27-5). Most of its cells are comparatively large.[356] Medially at more caudal levels, this nucleus abuts against the posterior hypothalamic nucleus. Here the tuberomamillary nucleus is coextensive with the posterior nucleus through a bridge of cells, the perifornical and intrafornical nuclei.[447]

Bulging from the inferior surface of the hypothalamus laterally are two or three spherical or oval, sharply defined cell aggregates, the nuclei tuberis laterales.[243] Each is invested in a "capsule" of fine fibers. Superiorly these nuclei are bordered by the tuberomamillary nucleus; rostrally they approximate the posterior end of the supraoptic nucleus; caudally they approach the mamillary body.

HYPOTHALAMIC SURROUNDINGS, INCLUDING THE LIMBIC SYSTEM, AND PATHWAYS TO AND FROM THE HYPOTHALAMUS

Most of the fiber systems passing into the rostral part of the hypothalamus come from the limbic lobe, while the systems extending into the caudal hypothalamus come from limbic midbrain nuclei and other midbrain cell aggregates. Moreover, some fiber systems reaching the hypothalamus caudally are closely identified

with cell groups of the brain stem reticular substance.

The limbic lobe, a fairly large part of the cerebrum, is made up of two rings of cortex, an inner and an outer, the latter bordering the rest of the cerebrum (Fig. 27-6) (hence limbus, border or threshold). The inner ring, phylogenetically the older, includes several structures: hippocampal formation, septal and parolfactory areas, anterior perforated substance with its olfactory tubercle, and the piriform cortex and adjacent part of the amygdala (cortical and medial amygdaloid nuclei). The outer ring includes the orbitoinsulotemporal cortex rostrolaterally, the cingulate cortex superiorly, and the entorhinal cortex (cortex of hippocampal gyrus) and subiculum inferiorly. The olfactory bulb and other rhinic structures project fibers into various components of this system.

Fig. 27-6

Taken as a whole, the limbic lobe appears to function in the execution of primitive semiautomatic sequences of action,[441] in the realms of affect and sexual function and their somatic and autonomic accompaniments,[362,365] and in the cognitive sphere.[378] The limbic lobe is organized more in terms of the elaboration and coordination of varied complexes of behavior, such as those mentioned, than in terms of precise and delimited physiological functions.[389]

The midbrain limbic system originates from nuclei in the paramedian part of the midbrain, including the dorsal and ventral nuclei of Gudden[400] (Fig. 27-7). It is concerned in hypothalamic-pituitary activation.[402]

Fig. 27-7

The largest fiber system reaching the hypothalamus is the medial forebrain bundle, a bundle which is to the limbic lobe what the internal capsule is to the neocortex. The bundle courses in the lateral preoptic and hypothalamic areas (Figs. 27-6 and 27-8). The cells in these areas are bed nuclei for the bundle in its entire hypothalamic course, and they compose a continuous longitudinal cell group interstitial to the medial forebrain bundle, with both areas generously contributing fibers to the system along its entire trajectory.[389] The

Fig. 27-8

bundle derives its fibers chiefly from the hippocampus, amygdala, piriform cortex, anterior perforated substance (with its olfactory tubercle), orbitofrontal cortex, and septal nuclei, and from brain stem sources to be dealt with later. En route through the preoptic and lateral hypothalamic areas some fibers of the bundle extend medialward and terminate in medial hypothalamic nuclei, principally the ventromedial nucleus.[540]

The hippocampus, which, as mentioned, belongs to the rostral group of limbic structures, projects chiefly by way of the fornix to the lateral preoptic area and the medial nucleus of the mamillary body as well as to septal nuclei and the habenular nuclei via the stria medullaris thalami. Some fibers by-pass the mamillary body and end in the rostral part of the central gray substance and the ventral tegmental area of Tsai (Figs. 27-7 and 27-8). Numerous fornical fibers also reach certain thalamic nuclei (anterior nucleus and rostral intralaminar and midline cell groups).

The amygdala and piriform cortex are also among the rostrally situated limbic structures. A system of fibers, the ansa peduncularis, originates both from the amygdala and the piriform cortex and passes medially through the region of the substantia innominata; here it divides into a fiber group bound for the medial thalamus (the inferior thalamic peduncle) and another group (the ventral amygdalohypothalamic pathway) which appears to disperse itself in the lateral hypothalamic area (Figs. 27-6 and 27-9). The ansa peduncularis conducts in both directions. It is a system of reciprocal associations between the components of a continuum of gray matter extending from the amygdala and piriform cortex over the substantia innominata and lateral hypothalamic area dorsalward into the medial thalamus. Through this system the lateral hypothalamic area apparently receives fibers not only from the amygdala and piriform cortex but also from the medial thalamus.

Fig. 27-9

Another amygdalar liaison is with the globus pallidus, thence via pallidal

and subpallidal pathways to the midbrain reticular arousal system.[5] Hence, both through hypothalamic and extra-hypothalamic relays the limbic lobe exerts a powerful regulatory influence on midbrain nuclei and on reticular core systems involved in generating and sustaining vigilance behavior.

Another route by which the hypothalamus receives fibers from the amygdala is the stria terminalis. This is a robust fiber bundle that passes posteriorly from the amygdala, then takes a semicircular course to reach the region of the anterior commissure; from here, fibers course into the hypothalamus (to the preoptic, anterior hypothalamic, suprachiasmatic, ventromedial, and tuberinfundibular nuclei) and to the anterior perforated substance. Moreover, some fibers extend into the stria medullaris thalami for distribution to the habenular nuclei.

Both the amygdala and hippocampus send fibers to septal nuclei and the lateral preoptic area, which are considered nodal points in the limbic projection system.[389,400,403] From these nodal points, secondary fibers reach the medial and lateral tuberal regions of the hypothalamus, in the general vicinity of the infundibulum. Another nodal point in the limbic projection system is the mamillary body, which receives its heaviest contingent from the hippocampus. From the three nodal points - septal nuclei, lateral preoptic area, and mamillary body - fiber systems pass to the midbrain. Those from the septal nuclei and the lateral preoptic area course caudally in the medial forebrain bundle to end in various parts of the midbrain tegmentum, while those issuing from the mamillary body pass through the mamillotegmental tract to terminate chiefly if not entirely in the dorsal and ventral tegmental nuclei of Gudden. These comprise a ventral system, in contrast to a dorsal system which extends from septal nuclei via the stria medullaris thalami to the habenular nuclei, thence, via the fasciculus retroflexus to the interpeduncular nucleus. These ventral and dorsal systems have a dual distribution in the midbrain, a lateral component terminating in central and lateral tegmental regions, and a medial component in

medial and paramedial regions. Both represent a first link in widespread descending pathways to visceral motor nuclei, relaying multisynaptically in their descent through the reticular substance of the brain stem. Undoubtedly this downward discharge from the hypothalamus also profoundly affects non-visceral functions of the brain stem reticular formation, such as cerebral cortical activity and somatic reflex mechanisms.

Fiber pathways emanating chiefly from the medial component of the mesencephalic limbic system pass back to the mamillary body, lateral preoptic area, and septal nuclei (Figs. 27-6 - 27-9) and thus close a circuit concerned in limbic as well as in reticular substance activation, including activation of certain tuberal nuclei concerned in anterior pituitary functioning (the midbrain-hypothalamic-pituitary activating system). The ascending fibers in question originate in part in the dorsal tegmental nucleus of Gudden and in the more rostral central gray midbrain substance and follow Schütz's dorsal longitudinal fasciculus predominantly to the posterior hypothalamic and supramamillary and premamillary nuclei[403] and in less degree to dorsal hypothalamic nuclei and the caudal part of the lateral hypothalamic area.[402] Other fibers arise mainly in Gudden's dorsal and ventral tegmental nuclei and travel in the mamillary peduncle to the mamillary body, lateral hypothalamic nuclei, and septal area.[403,448] Such ascending pathways doubtless convey impulses from the brain stem reticular substance to the hypothalamus. It is likely that pain, temperature, and visceral-sensory impulses are thus conveyed. Both these afferent fiber categories are involved in hypothalamo-pituitary and hypothalamo-visceral mechanisms, such as those concerned in the responses to stressful situations, and may thus play major roles in the general phenomenon of endocrine and visceral homeostasis.

VASCULAR SUPPLY OF THE HYPOTHALAMUS

The arteries extending to the hypothalamus are derived from the anastomatic arterial circle of Willis, including its internal carotid and posterior cerebral

Fig. 27-10

arteries (Fig. 27-10). A secondary anastomosis is the arterial circuminfundibular plexus for the supply of the tuberal region and the neurohypophysis; its sources are the internal carotid and posterior communicating arteries.[130,147,256] The preoptic region receives its blood supply from the suprachiasmic artery, which usually springs from the anterior communicating. The hypothalamic vessels may be subdivided into anterior, intermediate, and posterior groups, which supply, respectively, the anterior, tuberal, and mamillary parts of the hypothalamus. In general, no specific nuclear arteries exist, as each nucleus or nuclear group in the hypothalamus receives its arterial supply from more than one vessel.[147] The supraoptic nucleus constitutes an exception, for it is supplied exclusively by a single artery, which comes either from the posterior communicating artery, the internal carotid, or the anterior cerebral artery. The tuberal region, as mentioned, receives tributaries from the superior hypophysial and posterior communicating arteries by way of the arterial circuminfundibular plexus. The more caudal part of the periventricular region is supplied by arteries that penetrate the posterior perforated substance and the region immediately lateral to the mamillary bodies.

The drainage of blood from the hypothalamus and vicinity is chiefly into the basal vein (of Rosenthal), through branches from the anterior perforated substance (anterior cerebral vein), the hypothalamus (postoptic vein and premamillary vein), and through the mediation of the interpeduncular venous plexus. The basal vein ascends through the cisterna ambiens and empties into the great vein of Galen or into the internal cerebral vein, though, on occasion, the venous blood passes from the interpeduncular plexus directly into immediately adjacent dural sinuses.

HYPOTHALAMO-HYPOPHYSIAL PATHWAYS AND VASCULAR SUPPLY OF THE HYPOPHYSIS

Terminology

Table 27-3

The terminology used in this chapter is indicated in Table 27-3. and in

Fig. 27-11

Figure 27-11. One of the chief difficulties in reaching terminological uniformity has been the varying depth of the infundibular recess in different animal species. The "infundibulum" (or "median eminence") is defined as that part of the neurohypophysis which contains capillary loops; it forms the floor of the third ventricle (in the region of the infundibular recess) and extends downward, merging with the infundibular stem, which contains no capillary loops.[256] The infundibular process, also referred to as the "pars nervosa" and the "neural lobe," is the expanded terminal part of the neurohypophysis. By "posterior lobe" is meant both the infundibular process and the adjoining pars intermedia of the adenohypophysis. The term "pars infundibularis adenohypophyseos" is preferable to "pars tuberalis of the adenohypophysis" because this part of the adenohypophysis is in contact with the infundibulum of the neurohypophysis, not the tuber cinereum.[518,519]

The infundibulum of many mammals, such as the cat, is divisible into two zones, the zona interna (or central part) and the zona externa (or peripheral part). The supraoptico(SO)-hypophysial tract courses in the zona interna of the infundibulum. The infundibular stem is made up almost wholely of the SO-hypophysial tract. The bulk of the infundibular process consists of zona externa. In man the infundibulum is a homogeneous structure, not divisible into zona interna and zona externa.

Vascular Supply of the Hypophysis

The hypophysis receives its arterial supply from the superior hypophysial and the inferior hypophysial arteries (Figs. 27-10 and 27-12).[147,374a,577,578] The infundibular process receives a conventional blood supply, in that its blood comes directly from an artery - the inferior hypophysial artery - and drains by way of veins into venous channels, which are situated in the fibrous connective tissue lining the sella turcica; the blood then enters the systemic circulation.

Fig. 27-12

The infundibulum receives its blood supply from the superior hypophysial

arteries. Some of these arteries descend through the pars infundibularis hypophyseos and form a capillary plexus which is situated on the surface of the infundibulum (the mantle capillary plexus) (Fig. 27-13). Capillaries proceeding inward from this plexus form capillary loops in superficial and deep parts of the infundibulum. Other branches of the superior hypophysial arteries course downward along the surface of the infundibulum, where they terminate in capillary formations. Side branches from the capillary formations as well as capillaries from the mantle capillary plexus join to form a capillary bed in the infundibulum, which is coextensive with the capillary bed in the hypothalamus. Direction of blood flow in this system is normally upwards from the infundibulum into the hypothalamus.[540,546] The lowermost part of the infundibulum receives its blood supply from two sources: the inferior hypophysial artery and a channel formed by an anastomosis between the trabecular artery (a branch of a superior hypophysial artery) and the inferior hypophysial artery. Capillary loops within this part of the infundibulum are formed in the manner illustrated in Figure 27-12. The capillary loops and other capillary formations (tufts, spirals, coils, convoluted capillaries in the form of spikes)[46,105,156,518,577,578] form the first (or primary) capillary bed; they drain into broad channels, the long portal veins, which upon reaching the anterior pituitary, divide into sinusoidal capillaries, called the second capillary bed. In reaching their destination, these portal veins course along the dorsal surface of the anterior pituitary, underneath the diaphragma sellae. From capillary loops in the lowermost infundibulum, short portal veins reach the anterior pituitary directly.[2,3] All the venous channels from the infundibulum that lead into the sinusoids of the anterior pituitary are referred to as the hypophysial portal system. Thus, most of the anterior pituitary is supplied by venous blood; the peripheral part of the anterior pituitary, by contrast, is supplied from small capsular arteries.

Fig. 27-13

Supraopticohypophysial Tract

The supraoptico(SO)-hypophysial tract originates from the supraoptic (SO) nucleus and the paraventricular (PV) nucleus, as well as from accessory ("supraoptic") nuclei situated between the SO and PV nuclei. This tract together with its cell bodies is aptly referred to as the magnocellular secretory system, to contrast it with the parvicellular secretory system next to be dealt with. Both the SO-hypophysial tract and its cells of origin contain neurosecretory material stainable by chrome alum hematoxylin or aldehyde fuchsin and they also exhibit a positive histochemical reaction for disulphide groups.[146,504,505,507,508] The fibers of the tract, which are coarse and nonmyelinated (except for some myelinated fibers in certain animal species), extend into the infundibulum. A considerable number terminate in the infundibulum, but by far the greatest number reach the infundibular process; at both sites they end on special capillary formations within islands of Greving (or Romeis[464]).

The neurosecretory material is synthesized in the perikaryon of SO and PV cells, flows downward in the axoplasm, and accumulates in the nerve endings in the islands of Greving preparatory to discharge into the circulation. The processes of astrocyte-like cells, called pituicytes, also end on the capillary walls;[46,464] some nerve fibers indent or even penetrate the cytoplasm of pituicytes in their course to capillary walls.[427,534-536] Through enzyme mechanisms, pituicytes are assumed to serve in the discharge of neurosecretory material (oxytocin and vasopressin) from the nerve endings into the blood stream.[340,534-536]

The components of the SO-hypophysial system in which oxytocin and vasopressin are carried remain undetermined because PV-hypophysial and SO-hypophysial fibers are so intermingled at the upper infundibular level that their respective origins and destinations are obscure. However, the observation (in man) that following stalk section relatively few cells in the PV nucleus undergo cytolysis (in contrast to cells in the SO nucleus) suggests that a large proportion of PV-

hypophysial fibers terminate in the infundibulum.[507]

Vasopressin (antidiuretic hormone) is discharged into the circulation under a great variety of physiological and pathophysiological conditions. Depletion of vasopressin and of stainable neurosecretory material from the infundibular process occurs following the administration of hypertonic saline or following the deprivation of water. Enlargement of cell bodies in the SO nucleus reflects this activity. In over-hydration, by contrast, an increased amount of neurosecretory material is found in the neurohypophysis.[169,340,507,508]

Tuberohypophysial Tract

The tuberohypophysial tract originates chiefly in the tuberoinfundibular nucleus of the hypothalamus. Since the cells of this nucleus are small, the nucleus and tract are called the parvicellular neurosecretory system. The tract, composed of fine, nonmyelinated fibers, proceeds into the infundibulum. In experimental animals some of the fibers have been shown to terminate on capillary formations in the zona interna of the infundibulum, while others extend into the zona externa to terminate on the surface of the infundibulum, in contact with the mantle capillary plexus. Venous drainage from all these capillary formations is by way of the hypophysial portal system. The neurovascular link as postulated for man is illustrated in Figure 27-13.

Neurovascular Link Between Hypothalamus and Anterior Pituitary

The neural control of the anterior pituitary is mediated by neurosecretory materials formed within the hypothalamus and conveyed to the anterior pituitary by the hypophysial portal system.[103-105,232,233,382,411,517,540] The tuberohypophysial tract forms the main neural component of the neurovascular link. Its nerve fibers terminate in relation to blood vessels, where many of them are separated from one another by the processes of pituicytes.

It has been suggested that two distinct types of neural control of the anterior pituitary exist. One is assumed to impart control through polypeptide

hormones (releasing hormones),[253] and the other through the release of monoamines at nerve ends within the infundibulum.[212] As revealed by a histochemical fluorescence method, the upper part of the infundibulum contains large amounts of primary catecholamines (adrenaline and noradenaline), with the highest concentration localized at the terminal endings of nerve fibers as they converge on the primary capillary plexus. An opinion offered is that the primary catecholamines, like the polypeptide releasing hormones, are transported to the cells of the adenohypophysis, and that both the catecholamines and the releasing hormones act as neuro-humoral transmitters for the regulation of activity of the adenohypophysis.[212]

Considered from the electron microscopy standpoint, it is known that both large and small fibers terminate on any one blood vessel and that dense core vesicles are the predominant organelle in the endings of both kinds of fiber. Large dense core vesicles are noted in some endings, and small dense core vesicles in others; they never coexist in the same ending.[66] Larger vesicles are assumed to contain neurosecretory material, possibly polypeptide hormones,[316] and the smaller vesicles primary catecholamines, as brought out with the use of fluorescence techniques.[212-214,317,480] Both kinds of vesicles are discharged into the blood stream under appropriate stimulation.

Identification of vesicles and other ultrastructural fiber components with releasing hormones has not been achieved. Nor has SO-hypophysial neurosecretory material been excluded as a releasing factor,[508] despite views to the contrary.[540] One could, for example, postulate that the considerable amounts of stainable chrome-alum-hematoxylin (CAH) material in the islands of Greving in the infundibulum, which contains vasopressin, are discharged into the hypophysial portal system. There has been some suggestion that CAH neurosecretory material is secreted in severely stressed rats, and that the vasopressin it contains functions as a corticotrophin releasing factor.[150] On the other hand, in rats

following removal of adrenals, thyroid, and gonads, dense core vesicles in the fiber terminals in the zona externa have been found increased in size and number, suggesting an increase in the production of ACTH-releasing hormone (or CRF) by the tuberohypophysial system.[11] After thyroidectomy or gonadectomy no dense core vesicle change was observed in terminals of the tuberohypophysial system.[11]

The concept that a distinct hypothalamic releasing hormone exists for each anterior pituitary hormone has thus not as yet found verification at the ultrastructural level. Nor is the problem settled in other aspects. The extraction and isolation of releasing hormones from hypothalamic tissue has been a difficult problem and is still unsolved.[485] Much criticism has been leveled against the methods of their assay. Errors in assay are inherent in the use of pituitary fragments in vitro where lack of control of the concentration of certain ions in the incubation media may affect the amount of ACTH or other hormones released, or when ACTH and growth hormone measurements are made in an animal in which the stress mechanism is not adequately controlled.[218,315,457]

Reactions to Stalk Section or Hypophysectomy

Section of the hypophysial stalk in young animals is followed by regenerative outgrowth of axons, so that a gross traumatic neuroma may form.[219,518] Less conspicuous regeneration may occur in older animals. Regenerated nerve fibers have been found in the infundibular region in hypophysectomized humans.[509] Despite regenerative capacity, stalk section in older animals may result in disappearance of 80 to 90 percent of the cells of the supraoptic (SO) nucleus and of a varying percentage - from 0 to 20 percent depending on the animal species studied - of the cells of the paraventricular (PV) nucleus. In studies of the human hypothalamus following stalk section progressive degeneration of SO and PV nuclei occurred, until, at the 6-month stage, most of the cells of both nuclei were severely atrophied while others had vanished; by 26 months hardly

any nerve cells remained in these nuclei except for smaller cells in the paraventricular nucleus.[57,58] Similar changes in these nuclei, including gliosis, have been noted in other studies.[360,390,453,454] Retrograde and other changes, but not cell loss, have been observed in the tuberoinfundibular and other nuclei following stalk section.[360]

Following stalk section in man, as much as 90 percent of the anterior lobe may be destroyed, through infarction brought about by severance of hypophysial portal vessels; however, the size of the infarcted area varies considerably regardless of the level of stalk section.[4,132,167,453,475] The same is true for the rat, cat, and other animal species.[2,130,131] In the hypophysectomized human the persisting part of the infundibulum sometimes becomes grossly infarcted, and sometimes not, and when not infarcted it may contain an abundance of "neurosecretory" material months afterward.[57,58,505,506]

FUNCTIONAL AND CLINICAL ASPECTS OF THE HYPOTHALAMO-NEUROHYPOPHYSIAL SYSTEM

Oxytocin and Vasopressin

The hypothalamo-neurohypophysial system includes the supraoptic and paraventricular nuclei and their fiber pathways in the infundibulum, the infundibular stem, and the infundibular process (the pars nervosa). This system elaborates and controls the release of two hormones: oxytocin, which causes contraction of the uterine muscle and expulsion of milk from the mammary gland, and vasopressin, which is the antidiuretic hormone (ADH). Both hormones have been isolated, their chemical structure determined, and synthesis achieved. They are octopeptides, of which six of the eight amino acids are common to both. The octopeptide of vasopressin is linked with a precursor or carrier polypeptide; both contain about 16 percent of cystine.[507] The molecular weight of beef vasopressin is 1084 and of oxytocin 1007. Vasopressin has been isolated in two forms: lysine vasopressin from hog pituitary, and arginine vasopressin from the pituitaries of other species, e.g., ox, sheep, and human. When stored in

the posterior lobe, vasopressin and oxytocin are linked to a protein, neurophysin. Purified vasopressin has very slight oxytocic activity, while oxytocin has no antidiuretic activity, at least not in man.

OXYTOCIN. Oxytocin acts in various ways. The stimulus of coitus appears to increase uterine contractions owing to oxytocin release,[148,191] and in this manner oxytocin may be instrumental in the transport of sperm. Oxytocin is also released in the male during coitus. The effect of the oxytocin may be to increase secretion from the accessory glands.[192] During parturition, distention of the cervix and the vagina stimulates the release of oxytocin which in turn induces strong contractions of the uterus. At the end of pregnancy and labor the uterus is far more sensitive to oxytocin than at any other time. In the absence of oxytocin, as in women with diabetes insipidus, labor may be abnormally prolonged and contractions weak. Injection of oxytocin restores uterine contractions to a normal pattern. During suckling, sensory stimulation of the nipples evokes reflex secretion of oxytocin, which induces contraction of the myoepithelial tissue of the mammary gland, resulting in milk ejection. Fright may abolish this milk ejection reflex, probably as the result of an outpouring of adrenaline. Oxytocin has been shown to increase the urinary excretion rate of sodium chloride in the rat and dog, but not in humans. There is considerable evidence to suggest that oxytocin is released from the neurohypophysis independently of antidiuretic hormone during pregnancy, labor, and lactation, as shown in studies on women.[108-110] Little is known of the feedback mechanisms through which the hypothalamus exerts an influence on the neurohypophysial release of oxytocin.[436] The problem at the anatomical level is also unresolved. The PV nucleus appears to be the main source of oxytocin (in the rat),[417] and there is evidence to suggest that oxytocin is carried by PV-hypophysial fibers, and vasopressin by SO-hypophysial fibers, though not exclusively so.[514]

VASOPRESSIN. Vasopressin is essentially an antidiuretic hormone (ADH) but

under suitable conditions it is also chloruretic and natriuretic, pressor, motor to intestinal muscle, and mildly oxytocic. As ADH, it acts on the mammalian kidney by increasing the rate of water resorption, mostly in the distal convoluted tubule, so that the osmotic pressure of the urine becomes raised above that of the plasma. The antidiuresis brought about by the administration of ADH occurs without any significant change either in glomerular filtration rate or in the rate of blood flow in the kidneys. The effectiveness of ADH in controlling the polyuria in diabetes insipidus is the same whether or not the kidneys are denervated. When given intravenously to anesthetized dogs, vasopressin elevates blood pressure. When it is injected subcutaneously into man the blood pressure does not rise and might even fall. A fall in blood pressure is presumed to be due to coronary artery constriction, since intense pallor of the skin and mucous membranes occurs in association with the fall in pressure.[436]

ADH is released from the neurohypophysis under a variety of physiological conditions. An increase in the osmotic pressure of the arterial blood or a decrease in blood volume will cause such release (see next Section). Emotional stress also induces an antidiuretic response, for example, in dogs exposed to an unpleasant noise or subjected to a weak pain stimulus. This effect is abolished by removal of the posterior lobe of the pituitary or by section of the SO-hypophysial tract.[477,551,552] Oliguria occurs during and following surgical procedures, an effect generally thought to be due to increased secretion of vasopressin in response to the stress of surgery. That this is the case has been clearly demonstrated through measurement of ADH level in the blood.[387] It has been found that during a surgical procedure such as gastrectomy the plasma vasopressin may rise from 1.7μU per ml. preoperatively to 146μU per ml. by the close of the operation, and then gradually fall until the normal level is reached by the fifth postoperative day.

There is suggestive evidence that vasopressin has a physiological function

in controlling vascular tone. Hemorrhage, for example, is accompanied by an increased excretion of vasopressin in the urine, and the same is true in the case of fainting.[436] As much as 1000 mU of pitressin given to normal human subjects may not raise blood pressure, whereas in persons with orthostatic hypotension the blood pressure will be raised by a dose of vasopressin as small as 1.0 mU/min i.v.[559] Generalized edema has been linked with excess secretion of vasopressin, causing water retention. Sodium retention associated with edema has been assumed to be due to excess secretion of aldosterone.[335] A strong argument against an increase in vasopressin is that patients with diabetes insipidus have been known to have generalized edema and ascites (author's observation). (For further discussion, see Section on Natriuresis and Inappropriate Secretion of Vasopressin.)

Role of Osmoreceptors and Volume Receptors in Vasopressin Release

Antidiuretic hormone (ADH) is produced by cells of the supraoptic (SO) and paraventricular (PV) nuclei and is transported into the neurohypophysis in the axoplasm of the fibers of the SO-hypophysial tract. An important determinant of ADH secretion and its release into the blood stream is the osmolality of the blood perfusing the anterior hypothalamus.[290,477,551,552] Small increases in blood osmolality cause a release of sufficient ADH to produce marked antidiuresis; conversely, small decreases in osmolality depress ADH release and lead to maximal water diuresis.

The term osmoreceptors has been proposed for those cells in the anterior hypothalamus that initiate the antidiuretic response.[552] In a study based on cellular electrical activity following injection of hypertonic solutions into the common carotid artery, cells exhibiting increased activity (osmosensitive cells) were found in the SO and PV nuclei, also in preoptic, septal, and midline thalamic nuclei. Originally the SO and PV cells were discounted as of importance in osmoreception because of the then current view that true receptors cannot

serve any other function.[122] Subsequently it was shown that a correlation exists between the rate of electrical discharge of individual nerve cells in the receptive area with changes in the amount of hormone released from the neurohypophysis,[83,281,537] suggesting that osmoreceptor cells and neurosecretory cells are one and the same. Evidence, both direct and indirect, now supports the view that the cells under consideration are magnocellular cells in the SO and PV nuclei and that both functions (osmoreception and secretion) are performed by the same cell. This is based on the following: (1) creation of a small supraoptic island by removing all other brain tissue leaves the water balance mechanism intact;[574] (2) fibers of the hypophysial stalk driven by electrical stimulation of the SO and PV nuclei increase their rate of firing while oxytocin is being released from the neurohypophysis;[281] (3) electrical stimulation of the neurohypophysis evokes antidromic potentials in SO nerve cells shown to be osmosensitive;[575] (4) a highly significant correspondence exists between the distribution of osmosensitive units and neurosecretory cells.[563] Osmoreception by cells in the SO and PV nuclei would be made possible by the very close approximation of the cell perikaryon to the capillary wall.

Volume receptor mechanisms for the control of vasopressin secretion have also been proposed, and the evidence is strong that such mechanisms exist.[532] Various investigators have reported that a sudden decrease in blood volume, such as results from hemorrhage, is followed by an increase in vasopressin secretion. Body maneuvers of various kinds also have this effect. Passive tilting of the body from a horizontal to an upright position may reduce urine flow by one half. Even changing from the standing to the recumbent position, or vice versa, will lead to changes in urine flow.[262] The left atrium and pulmonary circuit as well as other vascular circuits are possible receptor sites of volume regulation.[240] Tied in with this mechanism is aldosterone, which is concerned in the retention of sodium.

The SO and PV nuclei have been assumed to contain not only osmoreceptors but also volume receptors. The problem as to the central site of volume receptors has been approached through the ascertaining of the nuclear volume of cells in the SO and PV nuclei and in other diencephalic structures in animals subjected to isosmotic hypovolemia or to isosmotic hypervolemia. Alterations in nuclear volume of moderate degree occurred in the SO and PV nuclei, but the most pronounced change was in the subfornical and subcommissural organs. In animals given aldosterone the only significant increase in nuclear volume was in the pineal body. How the presumed volume receptor mechanisms in the subfornical and subcommissural organs exert an influence on blood volume is still to be ascertained.[429]

Hypothalamic Regulation of Drinking

The hypothalamus serves a dominant function in the balancing of water intake and output. In these functions the limbic system through its influence on hypothalamic functioning also plays a significant role.

A drinking center has been postulated as existing in the far-lateral hypothalamus at the level of the hypophysial stalk, just behind the "feeding center."[386] Evidence suggests that while water intake is inhibited in a medial area (destruction of which results in diabetes insipidus), it is stimulated by a mechanism in the lateral area.[512,541] Electrical stimulation of the hypothalamus of various animal species causes polydipsia. Stimulation in the goat revealed a drinking center that extended from the dorsal into the ventral hypothalamus from the level of the anterior commissure rostrally to the bundle of Vicq d'Azyr caudally.[24,28] Primary polydipsia has been demonstrated in dogs. In one study in which dogs were subjected to rostral hypothalamic lesions, hyperdipsia was sometimes the initial phenomenon, preceding polyuria by a day or two,[60] an observation supporting the concept of a drinking center in the more rostral hypothalamus. Conceivably, primary polydipsia may be attributable to

blockage of a releasing mechanism necessary to the entrance of antidiuretic hormone into the neurohypophysial circulation.[420] While water intake appears to be controlled by the hypothalamic centers mentioned, there is evidence to indicate that the limbic system is involved in drinking, both in the motivation of drinking (i.e., through "thirst")[193] and in transforming a need for water ingestion into appropriate behavior.[310] Lesions made in the septal area in the rat, for example, can evoke a diuretic effect similar to though less pronounced than observed following lesions in the SO or PV hypothalamic nuclei.[354]

Clinical Diabetes Insipidus

Diabetes insipidus in man is characterized by inordinate thirst, polydipsia, and by the passage of large amounts of urine. The thirst never seems to be slaked, not even at night. The specific gravity of the urine ranges from 1.000 to 1.005. The amount of urine excreted tends to vary from day to day, but usually averages 8 to 10 liters; the amount may be augmented by increased intake of salt and protein and lessened when these substances are taken in reduced amount.

Approximately 40 percent of the cases of diabetes insipidus are classed as idiopathic, heredofamilial with or without involvement of the supraoptico-hypophysial system, or due to some extrahypothalamic disease state. A fair proportion of cases of heredofamilial diabetes insipidus are sex-linked. In occasional instances of heredofamilial diabetes insipidus, in which the osmolality of the urine remains consistently low even after large doses of Vasopressin Tannate have been given, a congenital submicroscopic renal defect in water reabsorption in the loop of Henle and the distal convoluted tubule (nephrogenic diabetes insipidus) has been postulated.[572] Following saline infusion in a patient having this condition 32 percent more sodium and chloride and 300 percent more urine were excreted than by a control subject.[572] This implies preferential reabsorption of sodium and chloride as compared with water, and there is evidence

to suggest that the sodium is preferentially excreted by the ascending loop of Henle. In some cases of nephrogenic diabetes insipidus the mean length of the proximal convoluted tubules has been found about 50 percent less than normal.[135] In the light of this finding an interpretation offered is the following: Preferential excretion of sodium by the ascending loop of Henle so that a large volume of a hypotonic filtrate reaches the distal convoluted tubule, overwhelms the facultative reabsorptive capacity of the distal convoluted tubules (under the control of antidiuretic hormone) and results in the excretion of a large volume of dilute urine.[135] In some cases of hereditary as well as in idiopathic diabetes insipidus, sufficient loss of cells from the supraoptic nucleus and of large cells from the paraventricular nucleus has been found to account for the disorder.[235] Failure of the osmoreceptor mechanism has also been invoked as a basis.[370] Another form of diabetes insipidus, associated or not with active hepatitis is the result of abnormal ADH inactivation by various tissues, including liver tissue.[249,335]

Most of the remaining 60 percent of cases of diabetes insipidus are due to interruption of the supraoptico(SO)-hypophysial system by any one of a variety of pathological processes.[462] Skull fracture and posttraumatic arachnoiditis in the chiasmatic cistern, sarcoid, xanthoma, or a local inflammatory lesion may be responsible.[68,87,420] Rarely, diabetes insipidus is a complication of pregnancy; it may manifest itself during the immediate postpartum period, or its onset may be delayed for months or years; diabetes insipidus thus caused may be transient or permanent.[428] Tumors that may interrupt the SO-hypophysial system include glioma, craniopharyngioma,[409] implants from medulloblastoma, germinoma arising in the infundibular region,[124,221] and metastatic tumors. Under any of these conditions at least 80 percent of the SO-hypophysial system needs to be destroyed before permanent diabetes insipidus occurs.

The remaining small percentage of cases of diabetes insipidus are classed

as primary polydipsia, known also as compulsive water drinking. This condition develops in the absence of any demonstrable endocrine, renal, or central nervous system abnormality.[47,539] Intense thirst precedes polyuria in such cases.[211,306,568] Head trauma is frequently the precipitating factor. Children with diseases resulting in diabetes insipidus may subsequently have primary polydipsia, possibly related to psychogenic factors.[528]

Surgical division of the hypophysial stalk in the treatment of metastatic cancer often results in diabetes insipidus. The degree to which the SO-hypophysial system is destroyed determines the severity of the diabetes insipidus. With low stalk section the diabetes is minimal or absent; it is severe only when the median eminence or adjoining hypothalamic region is damaged.[490] Severity of the diabetes insipidus occurring after pituitary destruction by implanted Yttrium-90 has been found to correspond with the degree of cell loss in the supraoptic and paraventricular nuclei.[245] Diabetes insipidus usually fails to occur following hypophysectomy because remaining neurosecretory cells provide sufficient ADH for bodily needs.

PROGNOSIS. Prognosis depends on the nature and extent of the causative lesion. In hereditary diabetes insipidus, spontaneous improvement rarely if ever occurs. In diabetes insipidus resulting from trauma or encephalitis the diabetes may disappear though it is frequently permanent. Relief after surgical removal of a pituitary neoplasm depends on the degree of damage inflicted on the supraopticohypophysial system by the tumor or during the surgical procedure.

DIAGNOSIS. Polyuria and polydipsia occur under a number of conditions in addition to diabetes insipidus, for example, in psychogenic polydipsia, diabetes mellitus, hypercalciuria, hypopotassemia, and chronic renal disease.[462] A simple means of diagnosing diabetes insipidus is to withhold water to the point of discomfort and to observe the effect on the specific gravity of the urine; in diabetes insipidus the specific gravity is not expected to rise above 1.010.

This test is not always reliable because there is no standard end point and because marked dehydration may vitiate the results.

A more dependable test consists of hydrating the patient by administering water by mouth, 20 cc. per kilogram of body weight, and then giving, over a 45-minute period, an intravenous infusion of saline, 0.25 cc. per kilogram per minute.[271] Failure of antidiuresis to develop during or immediately after the saline infusion is evidence that an antidiuretic effect is lacking. Pitressin is given 15 minutes after the saline infusion is completed in order to determine whether the failure in antidiuresis is due to faulty production of the hormone or to refractoriness of the kidney to secreted hormone. Should Pitressin not produce an antidiuretic effect, the fault then lies in the kidney (as in nephrogenic diabetes insipidus) or is the outcome of widespread destruction of the tuberal region.[68] Polydipsia of psychogenic origin may be unmasked by this test. When diabetes mellitus and diabetes insipidus coexist, as occasionally occurs,[397,462] diabetes insipidus should be suspected if the polyuria persists after the diabetes mellitus has been brought under control by insulin.

TREATMENT. Posterior pituitary extract is effective therapy in most cases of diabetes insipidus.[227] Vasopressin USP (Pitressin) injected intramuscularly is recommended. The required dose will vary, but it ranges around 1 to 2 units per day. Also available for treatment is a long-acting preparation, vasopressin tannate USP (Pitressin Tannate), given intramuscularly, as well as posterior pituitary powder which can be sniffed. There are certain untoward reactions with vasopressin overdosage, e.g., increased intestinal activity with nausea, cramps, and the urge to defecate. The most serious reaction, particularly in patients with angina pectoris, is coronary constriction. The patient should not drink an excess of water following the administration of posterior pituitary preparations, since the antiduresis may result in water intoxication. Oral administration of the diuretic, chlorothiazide, or some other benzothiadiazine

analogue, markedly reduces urine volume, increases urine concentration, and alleviates thirst. The nephrogenic form of diabetes insipidus also responds to this form of medication. The response is paradoxical, for in normal persons the dominant action of the thiazides is to increase the renal excretion of sodium and chloride and the accompanying volume of water. Potassium supplement is given along with the thiazide. The only complication thus far reported is hypokalemia when the potassium supplement is inadequate. A patient stabilized on the diuretic therapy must be supervised, and serum and urinary electrolyte levels regularly monitored.[502]

Natriuresis and Inappropriate Secretion of Vasopressin

It is generally agreed that saline loading is accompanied, in many animal species, by an elevation in glomerular filtration rate (GFR). It is also recognized that changes in tubular reabsorptive capacity can occur independently of variations in GFR and appear to play an important role in homeostasis. Na^+ reabsorption in the distal part of the nephron is enhanced by aldosterone.

This hormone may also enhance Na^+ reabsorption at more proximal sites. Renal micropuncture experiments have provided evidence that a saline load causes a marked decrease in fractional tubular Na^+ reabsorption, and that this effect is independent of an elevated GFR. Furthermore, transfusion experiments[291,344] indicate that the reduction in tubular reabsorptive capacity may be caused by a humoral agent acting as a "natriuretic hormone" or by dilution of an "anti-natriuretic hormone."

Increase in natriuresis has been observed in goats following slow infusion of hypertonic NaCl into the third ventricle. This natriuresis was more pronounced when the animals were maintained on a NaCl-supplemented diet. The magnitude of the natriuretic response was dependent on the molality of the NaCl infused and on infusion duration. A much smaller relative increase in K^+ excretion occurred. The natriuretic response was not prevented by the admini-

stration of aldosterone, which normally decreases Na^+ excretion and increases K^+ excretion. Further, the natriuretic response could be elicited in goats in which diabetes insipidus was induced by median-eminence lesions, indicating that the release of ADH was not essential to the response. During the natriuresis the GFR was increased and the relative reabsorption of Na^+ was decreased. The time course of the development of the full natriuretic response was remarkably consistent and apparently independent of infusion duration, which suggested that there may be a humoral link in the natriuretic response. Certain further observations appear to have justified the assumption that the neurons which react to the infusion of hypertonic NaCl, leading to drinking, release of ADH, and natriuresis, are located near the third ventricle, probably in the hypothalamus. Variations in extracellular fluid volume rather than variations in extracellular Na^+ concentration per se were assumed to influence a hypothalamic mechanism responsible for the control of sodium homeostasis.[26] The view that the hypothalamus is involved in Na^+ homeostasis is also supported by the observation that acute lesions in the posterior hypothalamus prevent the natriuretic response to bilateral carotid artery occlusion.[114] Renal loss of Na^+ cannot be attributed directly to the action of ADH,[334] for if the fluid intake is restricted so that fluid retention and weight gain do not occur the serum remains normotonic with a normal Na^+ concentration, and renal sodium wasting does not occur.[283]

Hyponatremia and increased natriuresis may be associated with circulatory insufficiency and a contracted extracellular fluid volume (as observed in cases of fluid depletion and renal salt-wasting diseases), also in association with circulatory insufficiency and overexpanded extracellular fluid volume (commonly seen clinically in edematous patients). Hyponatremia may also occur in association with adequate circulation and expanded extracellular fluid volume. This type of hyponatremia, occurring in the absence of renal or adrenal disease, is

associated with inappropriate secretion of antidiuretic hormone (ADH) - "inappropriate" because ordinarily when the serum osmolality is low the urine formed is hypotonic, reflecting an increased excretion of free water in an attempt to return the serum to normal osmolality; the formation of urine hypertonic to serum with a normal GFR implies the presence of ADH.[283]

The salient features of the disorder are (1) hyponatremia and hypoosmolality of the serum and extracellular fluid, (2) continued renal excretion of sodium in spite of hyponatremia, (3) formation of urine which is less than maximally dilute and usually hyperosmolar to the serum, and (4) absence of evidence of dehydration, e.g., normal skin turgor and blood pressure.[283] Aldosterone secretion rates have been observed to be normal or suppressed.[292] The overriding defect in the disorder appears to reside in an increase in extracellular fluid volume. The increased volume leads in turn to increased GFR, diminishes proximal tubular reabsorption of water, and encourages an intracellular migration of both water and sodium.

CLINICAL FEATURES. The symptomatology, which is nonspecific, is attributable to the hypotonicity of the body fluids. The patient presents the manifestations of water intoxication, usually as the earliest signal of some underlying pathological process: fatigue, anorexia, headaches, nausea and vomiting, and progressive mental confusion. Subsequently there may be periods of hostility, violent behavior, and episodes of coma with convulsions, which may lead to irreversible brain damage.[348] The symptoms fluctuate from day to day in accordance with the concentration of sodium in the serum, the latter dependent on the vagaries of daily sodium and fluid intake. If the serum sodium falls below 120 mEq/l severe neurological symptoms and signs may develop. These include hyperventilation, muscle weakness, decrease or absence of deep muscle reflexes, Babinski sign, and bulbar or pseudobulbar palsy. A space-occupying lesion or a diffuse cerebral pathologic process may be suspected.[50,334,539]

CAUSATION. Inappropriate secretion of ADH occurs under a variety of conditions. Administration of long-acting vasopressin (Pitressin Tannate) is one of them.[334] Hypothalamic glioma in a 6-year-old boy was associated with a rise in ADH secretion together with somnolence and other symptoms related to tumor growth. In this case, bioassay of plasma ADH revealed a markedly elevated ADH level (53 μU/ml of plasma; normal values, 5-7 μU). There were certain unusual features about this case, e.g., hyponatremia was completely unresponsive to severe water restriction, so that the disorder in ADH output was atypical.[80] Chromophobe adenoma of the pituitary, head trauma, tuberculous meningitis, and intracranial aneurysm are other conditions in which inappropriate ADH secretion may be observed.[283] In some 35 percent of cases of epidemic St. Louis encephalitis the serum hyponatremia and hyposmolality observed were characteristic of the disorder.[571] The Landry-Guillain-Barré syndrome and porphyria are other conditions marked by these features. Diseases outside the central nervous system may also be responsible. In bronchial carcinoma, increased ADH-like activity having the characteristics of arginine vasopressin activity has been noted in the urine and plasma and in extracts of tumor tissue.[48] In certain intracranial diseases and in myxedema and porphyria as well as in "idiopathic" inappropriate ADH secretion ("diabetes tenuifluus") it appears that the ADH-like material emanated from normal sources but was influenced by abnormal control mechanisms.[283]

TREATMENT. Successful treatment of inappropriate ADH secretion depends primarily on reducing the extracellular fluid volume. This is accomplished by restricting fluid intake. Usually a fluid intake of 1000 ml. per day and a weight loss of several kilograms will accomplish this goal. Preliminary salt loading with hypertonic saline solution is of value only under conditions in which the patient presents symptoms of severe water intoxication (convulsions, coma). Underlying causes should also be eliminated, e.g., thyroxin for myxedema

and surgical resection of bronchial carcinoma.[50,283,348]

HYPOTHALAMIC REGULATION OF FOOD INTAKE; CARBOHYDRATE METABOLISM

The hypothalamus plays a decisive role in the balancing of energy intake and output in support of the body economy. In this function the limbic system through its influence on hypothalamic functioning also plays a significant role.

The ventromedial hypothalamic nucleus contains a so-called satiety center, i.e., a "stop eating" center. A cat will stop chewing and food will fall from its mouth during feeding when the ventromedial nucleus is electrically stimulated.[418] Bilateral destruction of this nucleus is followed by an abrupt onset of voracious food consumption.[270] In the rat, hyperphagia occurs immediately after operation, even before complete recovery from the anesthetic. The voracious eating may lessen in a few days, but even so the food intake is still abnormally high and the gain in weight averages 4 to 5 Gm. a day. This interval of overeating is designated as the dynamic phase. As obesity increases, the overeating diminishes and the body weight becomes stationary at a higher level than before the hypothalamus was damaged; this phase is called the static phase. If, after reaching the static phase, the animal is fasted until the body weight is back to the preoperative level, the dynamic phase returns, the animal eating voraciously until it has again become obese. Striking hyperirritability and increased motor activity are often exhibited at the beginning of the dynamic phase, but both decrease in intensity as the animals become obese, until lethargy finally ensues. There is a striking storage of fat, hypertrophy and dilatation of the gastrointestinal tract, and degenerative changes in the kidneys. The basal respiratory quotient is not significantly altered except during the dynamic phase, when the feeding of glucose raises it above unity, indicating a high rate of conversion of glucose to fat.[84,85] The pituitary is not necessarily involved in the production of obesity since this type of obesity

can be produced in hypophysectomized animals.[269]

The "satiety center" just discussed is functionally related to a feeding center. This "feeding center" is situated in the far-lateral hypothalamus in the same frontal plane as the ventromedial nucleus, and is connected with this nucleus by a fiber system.[33] With permanently implanted electrodes in the far-lateral hypothalamus, in the cat, stimulation for one hour daily for periods of five to ten days produced a tenfold increase in meat intake and an increase of milk intake as well.[151] Destruction of this specific area in cats and in rats is followed by an abrupt cessation of eating, even in those animals that had been rendered hyperphagic previously by damaging the ventromedial nuclei.[15] The aphagic animal does not necessarily abstain from eating because of a primary, generalized motor impairment, but, instead, through motivational deficit. This was brought out in a behavioral and anatomical study (in rats) that revealed a dissociation between aphagic and hypokinetic syndromes.[40]

It has been postulated that the urge to eat ("hunger") originates at the hypothalamic level and that the modification of food intake through a discriminative mechanism ("appetite") is a function of limbic structures in the temporal and frontal lobes. Be that as it may, the amygdala appears to have an excitatory influence on food intake, for aphagia (and adipsia as well) lasting five months has been encountered in a dog after complete removal of the amygdala bilaterally.[93] Electrical stimulation of the intact amygdala does not evoke consumatory behavior in the satiated animal but does affect food intake when the latter is in progress, suggesting the presence of secondary or modulator systems in this region which influence the primary systems.[242] The orbitofrontal cortex is clearly concerned in the quantitative consumption of food (in the monkey): a lesion made caudally in this part of the cortex serves to reduce food intake, while a lesion nearby will increase food intake.[18] As to the neocortex other than orbitofrontal cortex, it appears to be involved in qualitative

modification of food intake.

Carbohydrate metabolism fits into the scheme of hypothalamic regulation of feeding, inasmuch as the hypothalamus is specifically sensitive to the glucose reaching it. A hypothalamic glucoreceptor mechanism has thus been postulated.[373] On food ingestion or on administering glucose intravenously the electrical activity of the ventromedial hypothalamic region (the "satiety center") increases, and glucose utilization, as based on A-V difference, also increases. Conversely, on food deprivation, or on creating hypoglycemia, both electrical activity and glucose utilization decrease. Simultaneously, electrical activity in the far-lateral hypothalamus (the "feeding center") tends to vary in the opposite direction.[16,19,373] The rate of the blood sugar fall rather than the absolute glucose level appears to be the major determinant in the hypothalamic response.[456] Occurring in association with the increase in electrical activity of the ventromedial nucleus when blood-glucose level and glucose utilization are increased is an inhibition of gastric hunger contractions; following destruction of the ventromedial nucleus the inhibition is no longer evident.[491] These are all short-term effects. For long-term control related to the maintenance of normal body weight the existence of liporeceptors has been postulated.[307]

Electrical stimulation or damage at various levels of the neuraxis results in alterations in blood-glucose level. Blood-glucose level (in cats) has been increased on electrically stimulating the posterior hypothalamic and mamillary regions medially and the anterior and tuberal regions laterally. Blood glucose level is decreased on stimulating the anterior and tuberal regions medially.[17] In general, however, acute lesions in the hypothalamus, especially in the region of the paraventricular nucleus,[49,279] and elsewhere in the neuraxis (including the floor of the fourth ventricle in the region of the dorsal nucleus of the vagus) tend to produce hyperglycemia and glycosuria.[49,137] The glucose increase is generally considered due to activation of the sympathico-adreno-

medullary system, glycogenolysis in the liver being accelerated through the medium of sympathetic fibers passing to that organ, and glucose in the liver being mobilized by adrenaline. Transection of the midbrain (in dogs), by contrast, decreases carbohydrate metabolism, as reflected in a diabetic type of glucose tolerance curve.[23] The mechanism involved needs yet to be clarified.

In what way the hypothalamo-pituitary system contributes to carbohydrate metabolism is not clear. It has been postulated that under acute hypoglycemic conditions, hypothalamic glucoreceptor neurons (particularly those in the ventromedial nucleus) trigger not only autonomic discharges but also the release of ACTH[372] and growth hormone,[223] the latter of which appears to antagonize insulin. Section of the hypophysial stalk in animals produces no derangement in carbohydrate metabolism. Stalk section in patients with hormone-dependent cancer, a procedure that ordinarily eliminates much of the anterior lobe through infarction, has little effect on the diabetes, though occasionally the glucose tolerance curve tends to be flattened.[167] Stalk section in diabetic patients can, however, reduce the insulin requirements by as much as 50 percent, an effect presumed to be due to depression in the rate of pituitary diabetic factor, possibly growth hormone.[355]

In diabetes mellitus, small lesions of a degenerative nature have been found in the hypothalamus and/or infundibulum. These are probably caused by the diabetes rather than the reverse. It is interesting that in diabetes mellitus there may be an increased appetite despite high blood sugar. In explanation of this paradox it has been suggested that glucoreceptor cells in the hypothalamus, unlike neurons elsewhere, require insulin for the uptake and metabolism of glucose.[527] Insulin-resistant diabetes mellitus has been noted in cases in which a cyst or tumor of the midbrain or diencephalon was found at autopsy. Insulin-resistant diabetes of considerable severity was associated in one case with a pendulous cystic tumor attached to the roof of the third ventricle. The

tumor was presumed to have obstructed the interventricular foramina intermittently. The conclusion reached was that the diabetes and the cyst were probably not coincidental but that chronic neural excitation in this region induced by the cyst may have brought about a sympathetic hyperglycemia that aggravated the diabetes.[97] In another diabetic with a cyst in the pulvinar of the thalamus that obstructed the rostral orifice of the cerebral aqueduct, the diabetes grew worse with each acute exacerbation of internal hydrocephalus and improved as the intracranial pressure subsided.[406] In a clinical study of 54 cases of colloid cyst of the third ventricle, four showed hyperglycemia.[579] This incidence is high when comparison is made with other intracranial tumors except for acidophilic adenoma of the pituitary.

FUNCTIONAL ASPECTS OF THE HYPOTHALAMO-ADENOHYPOPHYSIAL SYSTEM

Effects of Hypophysectomy; Functional Properties of Anterior Pituitary Cells; Hormones Involved

When the adenohypophysis is completely removed from young animals skeletal growth stops except in the newborn, in which growth may continue for a short period of time. The brain continues to develop in the absence of the pituitary. The epiphyses of many of the long bones remain open for an extended period, eruption of teeth is delayed, and skin and hair remain infantile. In adult animals, spontaneous food intake decreases and there is loss of body weight, as much as 25 percent of weight in 2 to 3 months (in hypophysectomized rats).[570] The thyroid gland and the adrenal cortex become atrophic and their functions are reduced as much as 90 percent below normal. The gonads also atrophy, with resulting involution of the secondary sexual organs. When the hypophysectomized animal is fasted, the excretion of nitrogen in the urine is reduced below that of the starved normal animal, and since the power of converting protein to carbohydrate is virtually lost, hypoglycemia occurs during fasting, and may be fatal. There is also an increased sensitivity to insulin. Hypophysectomy in

a pancreatectomized animal greatly ameliorates the course of the diabetes. These disturbances are caused by the loss of the hypophysial hormones: growth hormone (somatotrophin, STH, GH), thyroid-stimulating hormone (thyrotrophin, TSH), adrenocorticotrophic hormone (ACTH), two gonadotrophic hormones [follicle-stimulating (FSH) and luteinizing (LH)], also lactogenic hormone (mammotrophin) and melanocyte stimulating hormone (melanotrophin, MSH).

The anterior lobe of the pituitary is composed of cords of epithelial cells surrounded by sinusoids and supported by a connective tissue stroma. Examination of sections stained by hematoxylin and eosin reveals two main types of cells: chromophils, which take up the stain differentially, and chromophobes, which take on a neutral color. The chromophils are divisible into acidophils (eosinophils) and basophils.

Data derived from studies on experimental animals with the use of special staining techniques and with the electron microscope give support to the concept that cells of the anterior pituitary go through secretory cycles and that there is a specialized cell responsible for the production of each hormone.[405,445,476] The acidophil cell has been considered the source of growth hormone ever since the early finding of acidophilic adenoma in patients with acromegaly or gigantism. Growth hormone has been demonstrated within the acidophils of the human adenohypophysis by staining with a fluorescent-labelled antibody to human growth hormone.[342]

Recognition of the glycoprotein nature of TSH, FSH, and LH, and the demonstration of the glycoprotein nature of basophil granules, has led to the belief that each of these three hormones is secreted by its own specialized type of basophil cell. ACTH is also supposedly secreted by a certain type of basophil cell and/or by large chromophobes (degranulated basophils, neutrophil cells). A cell referred to as the "pregnancy cell" is believed to secrete the lactogenic hormone because of the changes it undergoes during pregnancy. Cells

of the pars intermedia (beta basophil cells) have been shown by tissue culture techniques to produce the melanocyte stimulating hormone (MSH).[22]

SOMATOTROPHIN (GROWTH HORMONE, STH, GH). Growth of an animal involves a multitude of biological reactions but the key to this mechanism appears to be the growth hormone. The first evidence of the existence of a growth hormone was that extracts of bovine pituitaries could produce gigantism in rats.[179] This hormone has been under intensive investigation ever since, and today a good deal is known of its physicochemical properties. The chemical structure of the hormone varies with the species and accordingly the hormone from one species may have no biological effect on another species. As far as we know, only human growth hormone is effective in man.

Growth hormone acts chiefly on the supporting structures of the body, namely skeleton, musculature, connective tissue, and skin. This is most striking in acromegaly, where excessive growth hormone is responsible for pronounced deformities of the face, head, and skeleton. The biological effects of growth hormone involve not only protein synthesis but also carbohydrate and lipid metabolism.

The development of a method for the assay of growth hormone in blood by a radioimmune reaction has brought out some interesting findings regarding growth hormone secretion in the monkey[314] and in man.[468] A variety of stresses, e.g., exercise, anxiety, surgical procedures, and hemorrhage as well as hypoglycemia and fasting will cause a rise in the blood level of growth hormone. There is a rhythmic fluctuation of the hormone level throughout the twenty-four hours, but the level is highest at night. Women have a consistently higher level than men. The physiological significance of these diurnal and sex differences is not clear.

There is considerable evidence that the hypothalamus produces a hormone for the release of STH from the anterior pituitary. In monkeys, electrical

stimulation of the hypothalamus results in an increase in the mean plasma concentration of STH (radioimmune method) when some areas are stimulated, and a decrease on stimulation of other areas.[246] Weanling kittens subjected to hypothalamic lesions have exhibited a slowing of growth for as long as 14 months, however only when the paraventricular nucleus was damaged.[412] The limbic lobe is also concerned. Findings following lesion placement in the amygdala (its medial part) in deermice have allowed the conclusion that the lesions interfered with the secretion of hypothalamic STH-releasing hormone and resulted in increased storage of hypophysial STH and a probable decline in circulating STH.[171] Evidence that the hypothalamus produces a hormone for the release of STH from the anterior pituitary is also cited later in the text under Pituitary Dwarfism and under Acromegaly.

ADRENOCORTICOTROPHIN (ACTH). The observation that removal of the pituitary in experimental animals was followed by atrophy of the adrenal cortex led finally to the demonstration of adrenocorticotrophic hormone in extracts of the pituitary.[112] Intensive study then led to the isolation of the hormone, the elucidation of its chemical structure[343] and, finally, its synthesis. Minor differences in molecular structure have been found in the ACTH of different species, but in every instance the hormone consists of a single polypeptide chain of 29 amino acid residues. ACTH from several species (beef, pork, lamb) is effective in man.

The adrenal cortex produces several steroid hormones but the three important ones are (1) cortisol (hydrocortisone), having metabolic functions, (2) aldosterone (a mineralcorticoid), which acts directly on the kidney where it decreases sodium excretion and increases potassium and hydrogen ion excretion, and thus is concerned in the maintenance of blood volume, and (3) dehydroepiandrosterone, having androgenic function. 17-ketosteroids in the urine represent degradation products of the androgenic hormones from both the adrenal

cortex and the gonads, and 17-ketocorticoids, degradation products of cortisol.

Hypothalamic control of ACTH function has been extensively studied. In rabbits it has been shown that bilateral electrolytic lesions in the posterior tuberal region prevent the ACTH release that normally occurs following emotional stress.[149] In the cat and rat, lesions in the median eminence abolish ACTH response to stress. Thus, it has been shown that when normal animals are stressed (by cannulating the adrenal vein), adrenocortical hormones in adrenal vein blood increase (as determined by bioassay) and lipid and ascorbic acid in the adrenal cortex become depleted; when, however, animals with lesions in the median eminence are similarly stressed none of these changes occurs.[333,374]

In animals in a resting condition, ACTH continues to be released from the adenohypophysis even when the neurohumoral connections in the median eminence have been severed.[374] Destruction of the median eminence does not induce the degree of adrenal cortical atrophy observed after hypophysectomy and there are none of the severe signs of adrenal insufficiency. It would seem, therefore, that hypothalamic function in this connection is concerned chiefly with the rapid release of ACTH in response to stressful stimuli. No general agreement exists as to the site in the hypothalamus that initiates the ACTH-releasing mechanism, nor, despite extensive testing, has the ACTH-releasing hormone been isolated.[153] Wherever the nerve fibers may arise they must pass through the median eminence to make contact with capillary formations that drain into the hypophysial portal system. The median eminence is the one site where a lesion invariably blocks the ACTH-releasing hormone.

Functional alteration of the hypothalamo-hypophysial mechanism concerned in ACTH secretion is influenced by a number of outlying neural structures, including the limbic lobe. For example, secretion of ACTH is enhanced by electrically stimulating[371] or damaging[173] the amygdala. By contrast, in dogs studied over a considerable period of time after midbrain transection, which

interrupts mesencephalic pathways extending to the tuberal region, the release of ACTH in response to stressful situations is blocked.[20]

Studies carried out on women following infundibular stalk section for hormone-dependent mammary cancer have revealed marked depression in the output of ACTH, as based on determinations of 17-hydroxycorticoids in the serum and 17-ketocorticoid and 17-hydroxycorticoid excretion in the urine.

Certain tests are available for the detection of lesions at the hypothalamic or pituitary level that interfere with ACTH secretion. The tests are designed to ascertain the functional reserve of the hypothalamo-pituitary-adrenal axis to acute stress in terms of plasma cortisol level or the level of 17-ketocorticoid in the urine. (1) Pyrogen test. Salmonella polysaccharide pyrogen (Pyrexal) or some other type of pyrogen is used. (2) Vasopressin test. Lysine-vasopressin is ordinarily used. (3) Insulin tolerance test. Crystalline insulin is given, and blood sugar and plasma cortisol are determined. In normal subjects all three tests reveal significant increments of plasma or urinary corticoids. The methopyrapone (Metopirone) test may also be used but the results may be influenced by a number of systemic disease states.[247] In testing patients having a disease involving the hypothalamo-pituitary-adrenal axis, negative responses to testing usually correspond with the clinical findings and the other laboratory evidence of hypopituitarism. At least two of the tests should be used on any given patient in the evaluation of the status of hypothalamo-pituitary-adrenal function.[98] None of the tests appears to be useful in the differential diagnosis between hypothalamic and pituitary lesions or tumors.[98,289,358,359,547]

THYROTROPHIN (THYROID STIMULATING HORMONE, TSH). The adenohypophysis elaborates thyrotrophin, which is necessary for optimal and maximal function of the thyroid gland. The first evidence that the pituitary possesses this function was obtained in tadpoles: atrophy of the thyroid followed removal of the pituitary; repair ensued with the implantation of pituitary tissue.[12]

Corresponding results were obtained in the rat.[511] Soon afterward it was found that thyroid function was reduced approximately 90 percent following hypophysectomy. Isolation of TSH then followed.[21] TSH has more recently been obtained in a highly purified state from various animal sources. This hormone has, however, been one of the most difficult to prepare in an unequivocally homogenous form. Thus, complete information regarding its amino acid content and molecular weight is lacking.

That the secretion of TSH is dependent in part on activity of the central nervous system has been demonstrated in a number of ways. (1) Whereas pituitary tissue transplanted under the median eminence in hypophysectomized rats maintains the thyroid in a normal functioning state (as judged histologically), pituitary tissue placed in another part of the body, or in the subarachnoid space remote from the median eminence and outside the range of the hypophysial portal vessels, does not maintain a normal functioning thyroid although function is greater than in the hypophysectomized animal.[238,254] (2) Lesions in the anterior hypothalamus or tuberal region lead to a reduction in the concentration of TSH in the blood,[129] indicating a decrease in function of the thyroid gland.[239] (3) Stimulation in the anterior part of the median eminence augments activity of the thyroid, as indicated by ^{131}I release.[255] (4) Hypothalamic control of TSH release appears to be under the influence of a mesencephalic neural mechanism, for midbrain transection in dogs blocks the release of TSH from the anterior pituitary.[20] (5) Lesions made in the medial amygdala interfere with the secretion of ACTH.[172]

In women who have had infundibular stalk section as therapy for hormone-dependent mammary cancer, TSH activity of the anterior lobe has been found greatly reduced in most cases, but not as strikingly as after hypophysectomy. This indicates that the hypothalamus normally influences the release of TSH. Evidence exists that there are humoral feedback mechanisms concerned in the

regulation of TSH secretion. The adrenal cortex plays a role in this respect, for extirpation of the adrenals enhances the effect of hypothalamic stimulation on thyroid activity, presumably by removing the inhibitory effect of adrenal steroids on TSH release.[91] Thyroxin is also implicated, for not only is there a direct feedback action of thyroxine on the anterior pituitary for the prevention of TSH secretion (a negative feedback system),[305] but also a feedback site in the anterior hypothalamus, in the region of the paraventricular nucleus, as suggested by the observation that bilateral lesions in this region depress ^{131}I uptake and release by the thyroid gland.[300]

In thyrotoxicosis (Graves' disease) the thyroxine feedback mechanism appears to be interrupted. The thyroid gland undergoes hypertrophy and hyperplasia, and the production and release of thyroxine are increased. The increased blood level of thyroxine appears to have no inhibitory effect on TSH release. The demonstration that electrical stimulation of the hypothalamus will induce a release of TSH from the pituitary despite the inhibitory effect of a rising level of thyroxine in the blood suggests that a hypothalamo-hypophysial mechanism may be concerned in the development of thyrotoxicosis.[255]

FOLLICLE STIMULATING HORMONE (FSH) AND LUTEINIZING HORMONE (LH) (the latter is also called interstitial cell-stimulating hormone, ICSH). The early observation that gonadal stimulation resulted from implants or extracts of pituitary tissue[511,582] was followed by the discovery of two gonadotrophic hormones, the one, FSH, which stimulates follicle growth in the ovary and spermatogenesis in the testis, and the other, LH (or ICSH), which acts synergistically with FSH to cause rupture and development of the ovarian follicle and secretion of estrogens, also the development of the corpus luteum from granulosa cells and the secretion of progesterone. In the male, LH is necessary for the development of the testis and for the stimulation of the interstitial cells (Leydig cells) to secrete testosterone. FSH and LH have been partially separated by chemical extraction, but

no success has been achieved in preparing a biologically homogenous substance in the case of either hormone. There is another gonadotrophic hormone, not originating in the pituitary, namely, chorionic gonadotrophin, which is produced by the placenta. This hormone appears in abundant amounts in the urine of pregnant women.

The hypothalamus appears to exercise almost complete control over the release of FSH and LH from the pituitary, hence on gonadal function, as brought out in the following experiments on rats. Adult female rats with normal estrus cycles were hypophysectomized and their anterior pituitaries were transplanted into their own kidneys. During the three- to four-week observation period no estrus cycling occurred. The autotransplanted pituitaries of some of the animals were then retransplanted into their original site under the median eminence, and the animals studied for as long as 68 days. In those animals in which pituitaries had been returned to the median eminence, estrus cycles, which had been interrupted for a month, returned spontaneously; half these animals became pregnant. The thyroid and adrenal glands of these animals also showed significant increase in function. On the other hand, in those animals in which the pituitary remained in the kidney the ovarian follicular apparatus and the interstitial tissue were completely atrophied, indicating total absence of FSH and LH such as is seen following hypophysectomy. There was also marked reduction of thyroid and adrenal activity, although the reduction was not as pronounced as after hypophysectomy. Body weight remained essentially unaltered throughout the study, which may indicate that growth hormone was being released.[181,182,407]

The importance of the hypothalamus in sex maturation and sex differentiation has also been demonstrated by pituitary transplantation. Hypophysectomized female rats into which pituitaries from their own offspring (four to eight days old) had been grafted close to the median eminence had a resumption of estrus

cycles eight to thirty-five days after grafting,[254] which indicated that pituitaries from infantile rats are capable of stimulating the ovary at an earlier age than occurs normally when the pituitaries are left in their infantile bodies. It is well known that the ovaries of infantile rats can be stimulated by injections of FSH and LH long before the usual age of sexual maturity. These observations suggest that the state of the hypothalamus of the sexually mature animal, not the age of the pituitary or the ovaries, is requisite to the release of FSH and LH. That sex differentiation is a function of the mature hypothalamus has also been demonstrated.[238,254] When mature ovaries are transplanted into castrated male rats, large follicles develop, but they fail to form corpora lutea or to exhibit cyclic activity. This failure has been interpreted as evidence that the hypothalamo-hypophysial system of the adult male is not in itself capable of establishing the rhythmic fluctuation typical of estrus. A male hypophysis grafted close to the median eminence of hypophysectomized female is, however, effective in maintaining the normal estrus cycle and is instrumental even in the inception and maintenance of pregnancy.

There is some indication of the sites in the hypothalamus concerned in the regulation of pituitary gonadotropic function. Electrical stimulation of the tuber cinereum in the female rabbit evokes a discharge of LH with accompanying ovulation, while damage inflicted just behind the optic chiasm, in the region of the paraventricular nucleus, results in a state of persistent estrus, presumably by blocking the rhythmic discharge of LH.[154,155] The observation in the ferret that lesions placed basally and immediately behind the optic chiasm bring on premature secretion of FSH and early estrus suggests an FSH inhibiting mechanism in the anterior hypothalamus.[157] Preferential accumulation and retention of isotopic estradiol have been demonstrated both for the anterior pituitary and for certain sites in the hypothalamus both in the male and female.[170]

Two discrete hormone sensitive sites in the hypothalamus for the monitoring of circulating levels of gonadal steroids have been demonstrated in a number of male and female mammals: (1) the region of the arcuate nucleus, for the monitoring of estrogen titre and for bringing about tonic release of gonadotrophins from the pituitary via releasing hormones, and (2) the preoptic-anterior and mamillary regions, concerned in sexual behavior.[349,375] That specific neurons are involved in these functions is indicated by changes that occur in nucleolar size. It has been found, for example, that a correlation exists between nucleolar size in cells of the arcuate nucleus and the estrous cycle, and that following ovariectomy, changes occur both in arcuate and mamillary neurons.[275,276]

Uterine hypertrophy followed by ballooning, the appearance of a proestrous type of vaginal smear, vaginal opening and cornification and, ultimately, ovulation and the formation of corpora lutea,[176] occur in prepubertal female rats subjected to lesions of the anterior hypothalamus (sparing the arcuate nucleus) or to lesions of the medial part of the amygdala. The condition is analogous to that in human pubertas praecox. These observations support the view that the anterior hypothalamus has the capacity to inhibit gonadotrophin secretion and suggest that the amygdala may also be concerned in this function. That the amygdala is tied to sexual function is also indicated by the observation that hypersexuality develops in male cats upon removal of the amygdala, and is abolished by gonadectomy and then re-established by the administration of testosterone;[231,486] and, in the rabbit, that electrical stimulation of the amygdala induces ovulation.[321] Moreover, following removal of the temporal lobe bilaterally in the rhesus monkey, histological changes have been noted in the ovaries and the endometrium.[312]

By contrast, gonadal atrophy occurs following lesions which are made in the median eminence. This has been observed in the rat, guinea pig, dog, and rabbit. This location holds constant for both male and female.[349,517]

In women subjected to infundibular stalk section, the effects on ovarian function and reproductive capacity have varied, in one case having no influence,[128] and in others a suppressive effect.[167]

MAMMOTROPHIN (LACTOGENIC HORMONE, PROLACTIN). This hormone is necessary for the production and maintenance of lactation. The other pituitary hormones appear to have an important role as well. In humans it has not been possible to separate mammotrophin from growth hormone by chemical means. Release of prolactin (luteotrophic hormone) from the pituitary appears to be independent of hypothalamic control. If in rats the anterior pituitary is transferred to the kidney, prolactin is released at a normal or even increased rate, as indicated (1) by the maintenance of large corpora lutea, (2) by further enlargement of corpora lutea to "pregnancy size" when estrogen is administered, and (3) by vaginal mucification in response to excess estrogen.[182] There is evidence that oxytocin may stimulate the release of prolactin,[61] and if such be the case prolactin secretion would then be under the influence of the neurohypophysis. In women subjected to infundibular stalk section the function of lactation is fully preserved, and lactation may be increased.[167]

CLINICAL DISTURBANCES FROM INVOLVEMENT OF THE HYPOTHALAMO-ADENOHYPOPHYSIAL SYSTEM AND THE ANTERIOR PITUITARY

This section deals with a wide variety of clinical disorders, from pituitary dwarfism to states characterized by increased anterior pituitary function. The manifestations are not materially different from those induced experimentally in animals. Gonadal disturbances and obesity (or emaciation) characterize some of these disorders. They may occur independently of each other or together. When occurring together, the disorder is known as adiposogenital dystrophy; if the patient is preadolescent, the term "Fröhlich's syndrome" is applicable. Both obesity and gonadal failure result from lesions in the vicinity of the tuber cinereum, but it is evident from animal experiments that obesity is due to damage

inflicted on the ventromedial nucleus and environs, while gonadal failure results from damage involving the tuberoinfundibular nucleus and infundibulum. In the presence of hypothalamic lesions, obesity or emaciation sometimes dominates the clinical picture. It seems that the more widespread the hypothalamic destruction, the greater the likelihood that emaciation will occur; perhaps destruction of the far-lateral part of the tuber cinereum at the infundibular level may be responsible for emaciation, as in the rat.[14]

Pituitary Dwarfism

Less than 10 percent of cases of dwarfism are due to a lack of pituitary hormones. In "pituitary dwarfism," regardless of the cause, the manifestations may not appear until the child is a few years old. From then on, the bodily proportions remain infantile because of retardation of growth and maturation. Sexual development is lacking. The bone age is retarded. The increase in the concentration of plasma growth hormone that normally occurs in response to prolonging fasting (with hypoglycemia resulting) is usually lacking in pituitary dwarfism; the failure in response is a dependable criterion of hypopituitarism, and presumptive evidence of hypothalamic injury.[187,208]

Pituitary dwarfism due to overt damage in the pituitary tuberal region is probably most commonly seen in craniopharyngioma. To what extent damage of the hypothalamus is responsible for dwarfism, i.e., through interruption of a pathway carrying somatotrophin releasing hormone, is not known. That such interruption may be responsible in some cases is suggested by the findings in a 19-year-old dwarf with all the features of severe hypopituitarism commencing in childhood; the hypothalamus was found to be completely destroyed by a craniopharyngioma, whereas the pituitary was histologically "entirely normal." Emaciation also occurred in this dwarf, and although he ate three times the normal amount and devoured the scraps left on other patients' plates, the emaciation persisted. Diabetes insipidus and euphoria with manic episodes were additional features.[198]

Several forms of familial and genetic dwarfism are now recognized.[488] Familial dwarfism is characterized in some instances by isolated growth hormone deficiency,[488] in others by multiple pituitary hormone deficiencies.[187] In some cases, low excretion of 17-hydroxycorticosteroids in response to pyrogens occurs, indicating ACTH deficiency.[302] ^{131}I uptake by the thyroid may be reduced, and correctable, with the administration of TSH, suggesting TSH deficiency. Poor ability to maintain a normal blood sugar is a fairly frequent characteristic.[77]

The diagnosis of pituitary dwarfism, whatever the basis, should be confirmed by assay of growth hormone level in blood. Determination of growth hormone-induced nitrogen retention is also helpful.[88] Therapeutically, the administration of human growth hormone (2 to 5 mg. i.m.) has proved effective in younger children.[440]

A small sella turcica is noted in 10 to 15 percent of cases of pituitary dwarfism,[190] and thus the findings of small sella is suggestive of pituitary dysfunction but by no means specific. In familial or genetic dwarfism the sella is rarely reduced significantly in size.[187] A shallow depression rather than an actual sella turcica is occasionally encountered. Varied clinical disturbances have been noted in such cases, e.g., dwarfism, hypogonadism, obesity, and hypothermia.[357]

Simmonds' Disease, Sheehan's Syndrome

Both these conditions are characterized by an anterior pituitary insufficiency state. The term, Sheehan's syndrome, is applicable only when the pituitary insufficiency is the result of complications occurring in women around the time of parturition. The case Simmonds[499] first reported also falls into this category. His report dealt with a woman who, 11 years earlier, had had severe puerperal sepsis, and whose predominating clinical symptoms were weakness and emaciation. For this reason the term Simmonds' disease has come to by synonymous with "hypophysial cachexia." Anterior pituitary insufficiency is of varied

degree and has many causes. Cachexia of anterior pituitary origin occurs only when practically all the anterior pituitary tissue is destroyed, as brought out earlier in the chapter under Effects of Hypophysectomy.

Puerperal hypopituitarism (Sheehan's syndrome) becomes evident when 65 to 75 percent of the anterior pituitary is rendered necrotic.[493] The disorder may result from a number of complications occurring in the perinatal period, of which hemorrhage is the most frequent; other precipitating conditions include abruptio placentae, amniotic fluid embolism, placenta previa, septic abortion, and, occasionally, eclampsia. Shock or circulatory failure consistently occurs in patients in whom Sheehan's syndrome subsequently develops. Moreover, a definite correlation has been found between hypopituitarism and loss of blood during delivery.[496] The sella turcica in some cases is small, and the smallness may be of etiological importance inasmuch as the pituitary enlarges during pregnancy.[4,252,494] Rarely, diabetes insipidus is a feature of Sheehan's syndrome.[428] Specific arrest of the blood supply of the anterior pituitary in association with shock has been proposed as the basis of the syndrome in cases marked by severe puerperal hemorrhage.[498] Sudden hypotension associated with shock has been proposed as an alternative in some cases.[458] For the many conditions of systemic origin that can produce acute pituitary insufficiency, with chronic pituitary insufficiency ensuing, disseminated intravascular coagulation with fibrin emboli or bacterial endotoxins reaching the pituitary sinusoids (Shwartzman phenomenon), with shock resulting, has been proposed as the basis.[59,250] This view has not gone unchallenged.[324] Women who recover and who are given replacement hormonal therapy may subsequently have normal pregnancies.[284]

Approximately 25 to 75 percent of cases of anterior pituitary insufficiency fall into the category of Sheehan's syndrome, depending on the series studied.[184,494,497] Pituitary insufficiency due to other conditions are dealt with elsewhere in the text, for example, under chromophobe adenoma, craniopharyngioma,

and head trauma. Chronic basal meningitis, chordoma, metastatic or invasive carcinoma, and meningioma situated just in front of the anterior clinoid processes or along the medial aspect of the sphenoid ridge, are other conditions that may be responsible, as may also diabetes mellitus and epidemic hemorrhagic fever - to mention only a few.[324]

Anorexia nervosa needs to be considered in the differential diagnosis of Simmonds' disease. Anorexia nervosa is a psychological disorder characterized by voluntary, self-initiated dieting which gradually exceeds the limits of conscious control. The patient, with body image disturbances of delusional proportions, is in relentless pursuit of thinness. Marked weight loss, a fear of eating, overactivity, denial of fatigue, and a compulsive preoccupation with dieting, food, and weight are characteristic. In brief, the patient exhibits a never-ending coercive and manipulative struggle with the environment as it relates to eating.[92,228] Patients with anorexia nervosa are singularly unresponsive to conventional psychiatric treatment. An alternative psychotherapeutic approach has been found successful.[92]

Diencephalic Syndromes in Infancy and Childhood Due to Glioma

Profound emaciation is the chief manifestation of a diencephalic syndrome (called inanition syndrome, failure to thrive, athrepsia, or Russell's syndrome) observed in infants and children, from 2 to 6 months of age onward, in association with astrocytoma or some other type of glioma involving the anterior hypothalamus. The emaciation occurs despite normal or excess food intake. Appetite is frequently ravenous. The infant usually exhibits boundless energy and is jovial or euphoric, but occasionally is inert and indifferent and refuses food. The skin has a peculiar pallor, though no anemia exists. Nystagmus (to-and-fro oscillations of the eyes) occurs in about half the cases, and may be the presenting sign. Occasionally a tendency to hypoglycemia is observed, as is also an elevation in the serum level of growth hormone. Symptoms

and signs of an increase in intracranial pressure are foreign to this syndrome. Optic atrophy is sometimes noted. Increase in protein in the cerebrospinal fluid is another inconstant manifestation. Air encephalography commonly reveals deformation of the third ventricle.[38,102,107,510]

The survival period in infants with this syndrome is from 12 to 18 months. With treatment - cobalt radiotherapy or chemotherapy - survival may be for as long as ten years.[102]

Chromophobe Adenoma

Chromophobe adenomas constitute about 12 percent of intracranial tumors. The tumor develops almost exclusively in young adults, but persons having this tumor most frequently seek treatment when they are in their 40's.[175] Only about 4 percent are encountered in persons under twenty years of age.[36,567] Occasionally the tumor becomes clinically manifest in persons at an age as low as ten years.

Chromophobe adenomas arise most commonly in or near the hypophysial stalk. As an adenoma enlarges, it first compresses the pituitary, flattening it against the wall of the sella until, in some cases, only a shell of the anterior lobe remains. Simultaneously the sella turcica becomes ballooned. Erosion of the wall of the sella occurs only when the tumor becomes large, and anterior clinoid erosion only when the tumor extends laterally for some distance. The tumor may break through the diaphragma sellae and reach the base of the brain. Large extrasellar extensions of the tumor occur in 14 to 19 percent of cases[261,288] or in a smaller percentage.[471] Sometimes the adenoma produces disturbances from pressure on the hypothalamus and environs before significantly damaging the pituitary.

Chief among the clinical features are headache, manifestations of hypopituitarism, and signs and symptoms of compression of the optic chiasm. The headache may occur in earlier stages of tumor development. It is attributed

to tension exerted on the lining of the sella turcica and on the diaphragma sella. The headache may be bitemporal, but more commonly occurs in the region of the orbit and nose, unilaterally. Severe headache comes on suddenly if tumor infarction occurs, and under these conditions the headache is accompanied by abrupt deterioration of vision and impairment of consciousness.

Visual failure occurs as the tumor enlarges and is commonly the initial complaint. Reduction in the size of the visual fields is, however, greater than the degree of reduction in visual acuity. The inner lower part of each optic nerve is usually first compressed, leading to a defect in the upper outer quadrant of each visual field. This occasionally progresses to complete bitemporal hemianopsia, then total blindness. "Atypical" visual fields are very frequent; the defects may, for example, be asymmetrical on the two sides.[178] Occasionally the initial visual disturbance is homonymous hemianopsia.[36] Papilledema is rare.

Disturbances resulting from involvement of neighboring structures include anosmia, facial pain, and uncinate seizures. The third nerve is likely to be affected if the tumor extends upward and backward into the cavernous sinus, above the carotid artery. The palsy may involve, for example, the medial and superior recti and the levator palpebrae superioris, and spare or involve the intraocular muscles. In early stages the palsy may be intermittent owing to varying degrees of stretching of the dural sheath that contains the third nerve.[200] Diplopia without demonstrable extraocular muscle palsy, a complaint in some 40 percent of cases, with extrasellar extention of the tumor,[101] is attributable to the bitemporal field defects, which make accurate registration of the image in each eye difficult.[175]

In some cases damage of the anterior pituitary is such that Simmonds'

disease ensues and loss of weight may be preceded temporarily by obesity, owing presumably to damage of the tuberal region of the hypothalamus. Atrophy of the genitals occurs and amenorrhea develops in women and loss of libido in men. There is dryness and atrophy of the skin, loss of hair, muscular weakness, and increased sensitivity to cold; in addition, the heart rate is slowed, the blood pressure lowered, and the basal metabolic rate reduced 25 to 40 percent. The fasting blood sugar level is usually at the lower limit of normal, but severe hypoglycemia may occur if the food intake has been consistently very low. Moreover, there is reduced resistance to infection, noxious agents, trauma, and extremes of temperature.

Craniopharyngioma

Synonyms for craniopharynygioma include hypophysial-duct tumor, Rathke-pouch tumor, and adamantinoma, though the latter term is used to indicate a certain structural pattern of craniopharyngioma. Considering all intracranial tumors, the incidence of craniopharyngioma varies between 1.8 and 13 percent depending on the age group studied. Aside from chromophobe adenoma, craniopharyngioma is the most frequent tumor in the region of the sella turcica. This tumor usually becomes clinically manifest in childhood or in adolescence, but no age group is exempt; approximately 75 percent of the patients are under thirty years of age.

Craniopharyngiomas usually arise above the diaphragma sellae, somewhere along the course of the infundibular stalk, while others originate in the hypophysis. Some might have their origin in the basisphenoid.[409] It is generally held that craniopharnygiomas represent a neoplastic transformation of nests of metaplastic cells normally present in the region of the pars infundibularis adenohypophyseos.

CLINICAL FEATURES. The symptoms vary with the site of the tumor. When arising in the hypophysis, hypopituitarism usually results. Eventually the diaphragma sellae is penetrated, and on further growth the tumor may compress the optic chiasm and invade the infundibulum and hypothalamus, causing a variety of disturbances, such as optic atrophy, visual field defects, obesity, gonadal atrophy, and increased intracranial pressure.[409] Craniopharyngiomas of suprasellar origin usually lie behind the optic chiasm; initially, they involve the infundibulum and hypothalamus, then extend into the third ventricle (Fig. 27-14) or downward into the hypophysis. Symptomatology varies accordingly.

Fig. 27-14

When craniopharyngioma becomes manifest before the onset of puberty, the patient complains chiefly of headache and vomiting. Papilledema, of moderate degree, occurs in about 50 percent of the patients. Arrested sexual development is the rule, and there may be obesity. In both sexes, the subcutaneous fat has a characteristic infantile distribution, predominating about the thighs, hips, abdomen, chest, and face. Diabetes insipidus is rare in this age group. Growth is commonly retarded, and sometimes infantilism is predominant.

Young adult men with craniopharyngioma frequently have a history of endocrine disturbance from childhood. Aside from headache, the chief complaint is generally that of absent or failing libido. Reduced potency, eunuchoid facies, infantile body configuration, and feminine pubic escutcheon and high-pitched voice are characteristic. Young women are usually amenorrheic and overweight; the mammary glands are small and deficient in glandular tissue, and pubic and axillary hair sparse. In both sexes the skin is delicate, finely wrinkled, and pasty, and the hair scanty. Rotundness or obesity is common, but emaciation is sometimes

encountered. The basal metabolic rate is usually reduced. As a rule, the body temperature is lowered, but there may be bouts of hyperthermia. Manifestation of increased intracranial pressure become evident in approximately 35 percent of the patients, and diabetes insipidus, of varying duration, occurs in about 25 percent. Various forms of epilepsy may also occur.

Older adults complain mostly of headache and of failing vision. Evidence of increased intracranial pressure is infrequent. Endocrine disturbances are not as conspicuous as in younger persons; they include amenorrhea in the female, hypogonadism in the male with loss of libido, impotence, loss of body hair, and weakness. Mental and bodily sluggishness, somnolence, memory loss, and emotional instability are frequent. Diabetes insipidus occasionally occurs.

Optic atrophy develops in over 50 percent of the patients with craniopharyngioma irrespective of age. The initial visual field defect encountered is usually a paracentral scotoma in the upper temporal field on one side, then on the other. Subsequently, bilaterally dissimilar defects develop in lower quadrants of the visual field. Still later the defects may enlarge and include all the visual field except the upper nasal quadrant bilaterally. Central vision of one or both eyes is ultimately lost. Considerably less common are homonymous hemianopsia and concentric contraction of the visual fields. Unilateral central scotoma with or without any other visual field defect is a rarity, and difficulty is encountered in distinguishing it from the scotoma occurring in retrobulbar neuritis.[483]

Other clinical features, which depend on direction and degree of expansion of the tumor, include palsy of the sixth nerve, thalamic syndrome

and parkinsonian state,[549] hemichorea with or without hemiparesis, hemiataxia, and progressive exophthalmos.[393]

DIAGNOSIS. Pituitary dwarfism, hypopituitarism with or without obesity, optic atrophy, bitemporal hemianopsia, or diabetes insipidus, are conditions which should lead one to suspect craniopharyngioma. In the differential diagnosis, chief consideration should be given chromophobe adenoma. The age of the patient is helpful, since craniopharyngioma occurs most commonly in children and preadolescents, and chromophobe adenoma most commonly in adults. Diabetes insipidus is fairly common in craniopharyngioma in young adults, but is rare in chromophobe adenoma at any age; pituitary cachexia (Simmonds' disease) may develop in either. Although bitemporal hemianopsia occurs in both, the field defects tend to be symmetrical in adenoma and asymmetrical in craniopharyngioma. Roentgenography is helpful in differential diagnosis. Suprasellar calcification is almost never found in chromophobe adenoma but has been observed in 55 to 95 percent of craniopharyngiomas in different series.[409] The calcification is least frequent in older persons.[299]

Miscellaneous Conditions: Certain Other Tumors, Cysts, Archnoiditis, and Distention of the Third Ventricle

Suprasellar epidermoid tumors induce disturbances similar to those observed in craniopharyngioma. These tumors may be divided into two groups, chiasmal and tuberal. Bitemporal hemianopsia is the rule in the former group, and obesity and gonadal disturbances in the latter. A rarity observed in epidermoid tumor as well as in glioma of the hypothalamus is see-saw nystagmus.[369]

Glioma of the optic chiasm or optic tract leads to early visual failure and to a variety of visual field and optic disk changes. This

tumor occurs almost invariably in children and adolescents, and should be suspected when visual disturbances occur in generalized neurofibromatosis. Hypothalamic symptoms, including diabetes insipidus, are fairly common. Roentgenograms often disclose an expansion of one or both optic foramina (which may also be found occasionally in craniopharyngioma), hourglass deformation of the sella, or rarefaction at or near the base of the anterior clinoid processes.

Meningioma of the tuberculum sellae occurs almost exclusively in middle aged persons and frequently induces primary optic atrophy and slowly progressive bitemporal hemianopsia. Endocrine disorders are usually not present. Roentgenographically, the sella is normal, except, in some cases, for hyperostosis of the tuberculum and of neighboring bony structures, especially the upper part of the orbital fissure and the lateral margin of the optic foramen. Enlargement of the sella is also a rarity.[352] Retro-orbital aneurysms, by way of contrast, are characterized by erosion in these regions,[36] and rarely by enlargement of the sella.[352]

Intrasellar germinoma not infrequently arises in the chiasmal region, in which case it is commonly called "ectopic pinealoma." Or, in rare cases, a germinoma in the infundibular region represents a seedling from a pineal germinoma. Germinoma originating in the chiasmal region, characterized by visual disturbances, commonly extends into the tuberoinfundibular region, producing diabetes insipidus and hypopituitarism. Rarely the tumor extends into the pituitary, enlarging the sella turcica.[221,501]

Hypophysial-stalk cysts usually represent an enlargement of Rathke's cleft. Symptomatic cysts of this kind are relatively rare, and occur in various decades of life. In some cases, hypophysial cachexia prevails, and there may be diabetes insipidus. A greater proportion of cases are

characterized by signs and symptoms indicative of suprasellar location of the cyst. These include manifestations of increased intracranial pressure, progressive visual disturbances, bitemporal hemianoptic defects or loss of central vision on one side and a temporal defect on the other, bilateral optic atrophy, and, less commonly, impotence and diabetes insipidus.[67,381,489]

Opticochiasmatic arachnoiditis has bitemporal field defects as a hallmark,[561] but central scotoma and an atypical hemianoptic defect in the other eye are most characteristic of arachnoiditis in this location.[115] Polydipsia, polyuria, and obesity are also observed in this condition.[117]

Distention of the third ventricle, as in hydrocephalus, can also lead to bitemporal field defects and thus should be taken into consideration when pituitary or suprasellar tumor is suspected.[158,198]

Pubertas Praecox

Of all cases of pubertas praecox, 85 percent have been found in association with tumor of the adrenal gland or gonads, and the remaining 15 percent in association with intracranial lesions. Hypergonadism of intracranial origin occurs practically always in prepuberty males. The chief features in females are early appearance of the menstrual cycle and increase in the size of the breasts.[194] In the male, the disorder is characterized by enlargement of the external genitals, precocious libido, and premature growth of pubic, axillary, and facial hair. Bone age is advanced beyond the chronological age. Males may have extraordinary muscular development and phenomenal strength (macrosomia praecox). Boys as young as three years may have a deep voice and a well-developed mustache. The rapidity with which pubertas praecox may develop is illustrated by the case of a twin boy with a hamartoma involving the hypothalamus.

A very striking acceleration of growth and sexual precocity began at the age of four; at six years the boy was 58 inches tall and weighed 85 pounds.[531]

Many children with pubertas praecox are quiet and reserved, but some have a capacity for witticism. Others are mentally retarded. Children with pubertas praecox frequently have sexual interests far beyond their years, and thus become social problems. Emaciation rather than macrosomia praecox is apt to occur when the hypothalamus is seriously injured, as by an infiltrating glioma.[567] By contrast, obesity sometimes occurs in hamartoma.[484]

Cases of pubertas praecox of intracranial origin may be divided into two groups:[332] those occurring in association with hamartoma, and those related to a variety of other conditions, of which pineal tumor is the most frequent.[69]

When occurring in association with hamartoma, pubertas praecox sets in during early childhood, from about the age of a few months up to 6 years. Hamartomas, of which an example is illustrated in Figure 27-15, arise mostly from the tuberal region, just behind the infundibulum, and not infrequently from the mamillary body.[460,484,531] In hamartomas composed of cells foreign to the hypothalamus pubertas praeco has been lacking. In a fair proportion of cases of pubertas praecox associated with hamartoma, malformations are noted in other regions of the brain. Hypothalamic hamartoma now and then occurs in more than one member of a family. The development of pubertas praecox in the presence of hypothalamic hamartoma has been attributed (1) to excess production of a neurosecretory substance by hypothalamic nerve cells within the hamartoma,[163,383,484] (2) to an augmentation of hypothalamo-pituitary function through an excess of nervous

Fig. 27-15

activity set up in the hamartoma,[51] and (3) to deficit in mechanisms for neural inhibitory control of anterior pituitary function.[460]

Hamartoma removal can transform an "infant Hercules" into a normally slim boy and improve his mentality but not alter his sexual characteristics.[410]

Pubertas praecox arising in association with conditions other than hamartoma usually appears later in childhood. The hypothalamus is invariably damaged and, as a consequence, the pubertas praecox may be associated with polydipsia, polyphagia, obesity or emaciation, and somnolence.[74,339]

Pineal tumor, cyst in the third ventricle,[194] infundibuloma, ependymoma, craniopharyngioma, or chiasmal glioma may be responsible, as may also postmeasles encephalitis,[31] poliomyelitis, tuberculous meningitis, and opticochiasmatic arachnoiditis. In many of these cases the greatest damage is in the caudal part of the hypothalamus.[567]

Acromegaly

"Acromegaly" means an abnormal enlargement of the hands and feet, but in this disorder the entire body, the face, and the viscera are enlarged. The age incidence is from fifteen to fifty years, with the greatest number of cases in persons in their twenties. If the disorder begins before the epiphyses have closed, gigantism results; about 20 percent of acromegalics are giants.

Acromegaly is due to an overproduction of growth hormone (somatotrophin, STH, GH), produced by acidophil cells. Repeated measurements of STH throughout the twenty-four hours have revealed extreme variability in the levels in plasma STH, with the lowest values in the early morning. From these findings it has been suggested that the low plasma STH represents

basal secretion by the tumor and that the higher levels encountered during the daytime are attributable to an increase in STH secretion in response to hypothalamic stimulation. There is experimental evidence to suggest that provocative stimuli normally decrease STH output by the pituitary, a negative feedback phenomenon. In patients with acromegaly the reverse is true. This is taken as evidence of faulty hypothalamic control of STH release.[123] That the hypothalamus is responsible for increased STH release is indicated by the observation that such release is dependent on the integrity of the median eminence[1] and the hypophysial portal system.[468]

In most cases of acromegaly, an acidophilic adenoma is to be found, but there are cases in which no cellular abnormalities were observed and others in which the pituitary contained a chromophobe adenoma or ganglioneuroma.[30] An aneurysm compressing the hypothalamus was the only abnormality observed in another case.[87]

An acidophilic adenoma grows slowly and may ultimately break through the diaphragma sellae. It often attains sufficient size to compress the optic chiasm and, occasionally, the infundibular region. As an adenoma expands, it compresses and destroys the surrounding pituitary tissue. The loss of basophil cells is reflected in the sexual impotence and sterility that may occur. The sella turcica usually enlarges symmetrically, and the tumor may erode the floor of the sella and occasionally break through into the sphenoid sinus.

CLINICAL FEATURES. Headache, often bitemporal and frequently agonizing, is one of the first symptoms of acromegaly. It is believed to be due to the tension exerted on the diaphragma sella. The appearance of the patient gradually alters. The hands and feet become conspicuously

enlarged and the facial features coarsen. Prominent supraorbital ridges balance the enlarged cheek bones and lower jaw. The vertebral column also hypertrophies, and usually is kyphotic in the cervicothoracic region. The tongue grows almost too large for the mouth, sometimes making eating difficult. The skin becomes thick and wrinkled, and the hair coarse and profuse. The scalp may be thrown into folds. Sweating is increased. Widespread paresthesias and pains of a neuralgic character, owing apparently to increase in interstitial tissue in and around nerve trunks, are common.

Early in the disorder, glucose tolerance is usually decreased and there may be transient glycosuria. This is attributable to an increased production of growth hormone by the anterior hypophysis. In about 50 percent of acromegalics, this condition progresses to a frank insulin-resistant diabetes mellitus. Evidence of hyperthyroidism, assumed to be due to excess production of thyrotrophic hormone (TSH), may also occur early in the course of the disease. Hypergonadism, manifested by increased libido and hypertrophy of the gonads, may be present early in the disease, but gonadal function usually becomes depressed as the disease progresses.

Manifestations of pressure on the base of the brain are common. Chief among them are disturbances in vision. The tumor usually projects upward, just anterior to the optic chiasm, first compressing the lower decussating fibers and thus causing upper temporal quadrantanopsia, which progresses to a bitemporal field defect. Ultimately, central vision is lost. Occasionally, the tumor first compresses the lateral part of the chiasm, causing homonymous hemianopsia. The optic disks become atrophic. Extraocular muscle palsy occurs in about 10 percent of patients with acromegaly, the third nerve most frequently.[548] Involvement of the

hypothalamus is relatively uncommon. Pituitary apoplexy (hemorrhage into a rapidly growing tumor) occurs occasionally, and is manifested by sudden exacerbation of all symptoms and signs.[86,288]

Eventually, the hyperpituitary state passes into hypopituitarism, even without treatment. The patient complains of muscle weakness, constant fatigue, and mental depression. Other acromegalic features regress; subcutaneous tissues become thinner, hair falls out, sweating ceases, and glucose tolerance may return to normal. The basal metabolic rate may become subnormal. Gonadal atrophy, loss of libido, and amenorrhea invariably occur. The bony changes and other stigmas of overgrowth persist. (For treatment of acromegaly, see Chapter 9.)

Gigantism of cerebral origin in children is an uncommon condition, the main features of which are increase in height and weight with accelerated skeletal maturation and with mental retardation associated with anti-mongoloid slant of the eyes. Children with cerebral gigantism are well proportioned, though the hands and feet are large. Radiographic findings include slightly dilated ventricles and abnormal appearance of the dorsum sella. Extensive endocrinological studies have thus far not revealed any evidence of increased pituitary function. Glucose tolerance is normal. Persistent hyperthermia has been reported, and tests of autonomic function clearly point to central failure of temperature control. The cause of cerebral gigantism is assumed to be related to hypothalamic deficits.[32,384,526]

Cushing's Disease

This disease (or syndrome) is marked by obesity of peculiar distribution, hypogonadism, and by many other disturbances of a metabolic nature. It most commonly affects adults, women somewhat more frequently than men.

It also occurs in younger persons, also in infancy and even congenitally.

"Dyspituitarism" associated with pituitary basophilic adenoma was originally regarded as the cause of the disease,[127] until it was realized that increased secretion of adrenocortical hormones was the basis of the clinical syndrome.[258] Bilateral adrenal hyperplasia is noted in 50 to 70 percent of patients with the disease. Evidence now indicates that Cushing's disease results from inappropriate control and excessive secretion of corticotrophin releasing hormone (corticoreleasing factor, CRF) by the hypothalamus, in which the limbic system plays a prominent role.[346,351] This releasing hormone, when in excess, is assumed to bring about an increase in the output of ACTH from the anterior pituitary (hyperpituitarism thus exists); adrenal hyperplasia ensues and increased cortisol output gives rise to the metabolic and clinical stigmata of Cushing's disease. The regulation of CRF release by the hypothalamus through serum corticol levels (a positive feedback system) that normally occurs[351] is assumed to be defective in patients with Cushing's disease. The suggestion has been made that Cushing's disease is the outcome of a setting of the "CRF-ACTH-cortisol hormoneostat" at higher than normal levels. Inciting factors bringing the disorder into being remain unresolved.

A clinically demonstrable pituitary tumor is found in about 10 percent of cases of hyperadrenalcorticalism. Such tumors are more commonly composed of chromophobe than of basophil cells.[470] This may be related to transformation, brought about by CRF during the course of the disease, of basophils into large agranular chromophobes, recognized to be the producers of ACTH.

CLINICAL FEATURES. Cushing's disease in adults is characterized by

plethoric and painful obesity involving the abdomen (which becomes protuberant), shoulder and neck region and face, with a pad of lipomatous tissue along the lower part of the back of the neck ("buffalo hump"); a dusky appearance of the skin with purplish linea atrophica on the protuberant part of the abdomen and on the thighs; hypertrichosis of the face and trunk, amenorrhea in women and impotence in men. Osteoporosis, kyphosis, and lumbar pains are also noted. Other characteristic features are arterial hypertension, hyperglycemia, excessive appetite, and tendency to infection.[127] Another feature of Cushing's disease is weakness and atrophy in proximal limb muscles with secondary potassium depletion, a condition correctable by adrenalectomy.[437] Infants with Cushing's disease are overweight, have ballooned cheeks and buffalo hump, and fail to grow normally; occasionally they are hirsuit.[353]

Some 25 percent of the pituitary tumors occurring in patients with Cushing's disease have large extrasellar extensions, most of them in patients who had previously undergone adrenalectomy.[470,478] Visual disturbances and extraocular palsy occur in most of these cases. Occasionally, pituitary apoplexy (from hemorrhage into the tumor) develops, in which case all signs and symptoms suddenly become aggravated.

DIAGNOSIS. Diagnosis of Cushing's disease is made on the basis of the characteristic physical findings plus appropriate laboratory studies, including urinary levels of 17-ketosteroids and 17-hydroxysteroids. Adrenal cortical hyperplasia is distinguished from adrenal neoplasms with the help of the dexamethasone suppression test[345] and the methopyrapone (Metopirone) stimulation test.[224] Rarely, a tumor situated elsewhere than in the pituitary or adrenal, and presumed to be ACTH-producing, can give rise to Cushing's disease. In such cases the clinical manifestations respond

dramatically to massive doses of ethinylestradiol, while in classical Cushing's disease the response to estrogen is only slight.[408]

TREATMENT. Irradiation of the pituitary is commonly carried out in earlier stages of Cushing's disease. However, bilateral adrenalectomy is the operative treatment of choice in Cushing's disease (1) if the response to radiation therapy is unsatisfactory, (2) if adrenal neoplasm is suspected, and (3) if osteoporosis is advanced or if there is uncontrollable hypertension or severe psychosis.[322] Exogenous adrenal steroids are given postoperatively to prevent addisonian crises.

DISORDERS OF SLEEP AND WAKEFULNESS

Definition and Characteristics of Sleep

Sleep is a diurnal, rhythmically occurring state in which a person lies inert with consciousness suppressed so that he is out of touch with his environment. An essential feature is that the sleeping person can readily be aroused from his sleep.

Wakefulness, orthodox sleep (or "slow wave" sleep), and paradoxical sleep are the three states of the central nervous system recognized as existing in many vertebrates, with each state reflected in particular kinds of waves in EEG recordings. (The latter are dealt with in Chapter 3.) During sleep numerous reactions occur in the somatic and autonomic realms. A sleeping person exhibits decrease in muscle tonus and in proprioceptive responses and reflex irritability, increased movements of the eyes, constriction of the pupils, usually an abolition of tendon reflexes and, occasionally, the appearance of the plantar extensor response; arterial pressure, heart rate, and respiration are reduced (though they increase in the paradoxical phase of sleep); cutaneous and nasal mucosal vasodilatation occur, central core blood is cooled (and the rectal temperature

reduced) and cooling of the cerebral arterial blood and the brain also occurs;[259] electrical skin resistance is increased.[272,285,311,385] Sleep has not only negative components, e.g., suspension of consciousness, sensory functioning, and somatic motor activities, but also positive components. These include increase in total body oxygen consumption together with activation of central mechanisms concerned in restitution of bodily processes and the re-establishment of functional competence of the central nervous system.[264,266]

In a poor sleeper the rectal temperature does not fall as low as in a good sleeper, nor does the heart rate decrease as much; curiously, increase in electrical skin resistance is greater in the poor sleeper than in the good sleeper.[385]

Experimental Data

Experiments on the role of the hypothalamus in sleep-wakefulness were initiated through a study of the effects of lesions of its caudolateral portion. Lesions in this region bilaterally in monkeys resulted in a sleeplike state that lasted 4 to 8 days. During this period the animals had to be handled or shaken to be aroused. Animals surviving up to 21 days after the operation would, while eating, "go to sleep with the mouth full of food." The conclusions reached were (1) that some neural mechanism in the region of the third ventricle plays an important part in maintaining the waking state, both through upward drive on the thalamus and cerebral cortex and downward drive via the sympathetic system, and (2) that somnolence is chiefly due to the elimination of the downward hypothalamic drive, hence a passive phenomenon.[449,452] From another study, carried out on rats, in which transection was carried out at various levels - from the mamillary level forward - it was found that transection at the suprachias-

matic level resulted in irritability, hyperreactivity even to minor stimuli, and sleeplessness. The conclusion reached was that an anterior hypothalamic "sleep center" exerts an active inhibitory influence on a caudolateral hypothalamic "waking area," and that this influence is not exerted directly on to the cerebral cortex or on any other major structure.[399] Apparently, then, the agitation and sleeplessness encountered under such conditions is attributable to failure of the anterior hypothalamus, when damaged, to inhibit the activity of the caudolateral hypothalamus.[9] The import of these studies was the introduction of the concept that sleep is not entirely a passive phenomenon, but, instead, reflects elements of neural activation. That the anterior hypothalamus is influential in actively producing sleep was also brought out in an experiment in the cat, in which it was shown that electrical activation of this part of the hypothalamus produced spindle bursts and slow waves in the neocortex through the medium of specific relay thalamic nuclei, not by way of the midbrain. By contrast, an increase in the activity of the posterior hypothalamus abolished spindle bursts and slow waves and produced low voltage fast waves in the neocortex. These and other observations led to the conclusion that paradoxical sleep seems to involve activation of the posterior hypothalamus without the accompaniment of the anterior hypothalamus, on the one hand resulting in EEG activation of the neocortex, and on the other, producing characteristic changes in autonomic function during paradoxical sleep.[545] Finally, there is the observation, in the cat, that electrical stimulation in the ventromedial region of the hypothalamus inhibited electrical activity in the central and lateral mesencephalic reticular substance and resulted in synchronization of neocortical activity. A fully alert and active cat would, upon electric stimulation,

assume a state of relaxed wakefulness followed by a dozing state, then "postural" sleep. The EEG record in these situations usually show the high voltage slow wave pattern characteristic of light sleep.[389]

Emphasis is the investigation of sleep-wakefulness shifted to the reticular substance of the brain stem when it was shown that electrical stimulation of the central core of the brain stem, in cats asleep after transection of the lower medulla oblongata, resulted in the abrupt appearance of EEG and other signs of wakefulness.[392] Moreover, it was found (1) that after interruption of the tegmentum (especially in the region between the mamillary body and oculomotor nuclei) the animal behaved as though deeply asleep and exhibited cortical electrical activity characteristic of normal sleep, and (2) that awakening of the normal animal was dependent on impulses passing from the region of the reticular substance to the intralaminar nuclei of the thalamus and, in turn, to the cerebral cortex, as brought out by the EEG and the general behavior of the animal.[287,524] That interaction between reticular substance and various parts of cerebral cortex exists is supported by observations that fibers from cerebral cortical sources, limbic as well as sensorimotor, extend directly to the reticular substance.[203,330] The reticular substance includes not only the area in the brain stem already mentioned but also the dorsal hypothalamus, subthalamus, and ventromedial thalamus.[366,402,523] Initiation of alerting reactions is also a function of certain limbic structures (e.g., hippocampus, amygdala, and septal nuclei) through fibers relayed to the anterior nucleus of the thalamus and to the cingular cortex.[230,231,430] Electrical stimulation of both the amygdala and the globus pallidus (the two are interconnected; see Section on Hypothalamic Surroundings, etc.) can arouse a sleeping cat in a fashion resembling

that from stimulation of the reticular activating system itself.[94] The caudate nucleus is also a component of the "sleep circuit."[523] It has been suggested[78] that sleep may be a consequence largely of cumulative deafferentiation (or defacilitation) of the cerebral cortex through a lessening in the transmission of proprioceptive, exteroceptive, and other stimuli to the reticular substance and to the other structures mentioned - a view in accordance with the concept that sleep represents an active as well as a passive process.

Evidence has indicated that a considerable differentiation of function exists in different areas within the reticular formation of the brain stem. Thus, while a waking effect can be elicited by electrically stimulating the reticular activating system, situated in the upper midbrain,[367] areas exist in this self-same region in which sleep ensues following electrical stimulation. Stimulation in the vicinity of the red nucleus in a monkey was followed shortly by yawning, after which the monkey fell asleep.[444] Lesions, too, have an effect. Circumscribed lesions made bilaterally in the midbrain (in the cat) severely impaired attention and vigilance.[521] Lesions made in the upper pons have resulted in a waking, agitated state (with insomnia), with desynchronized rapid cortical activity, which has led to the hypothesis that normally the dorsal part of the medulla oblongata inhibits the midbrain-pontile activating areas.[9] Through studies of animals with lesions situated in the caudal brain stem, it has been proposed that a synchronizing or deactivating, hypnogenic influence is tonically exerted by cell aggregates in the caudal brain stem, either through active inhibition of the reticular activating system or by triggering thalamic synchronizing mechanisms, and that sleep ensues when the deactivating influences become strong enough to overcome

or supersede the antagonistic activating system of the brain stem.[391] Vago-aortic stimuli apparently lead to deactivation of the reticular activating system,[426] which implicates the region of the nucleus solitarius. There is strong evidence that the neural mechanisms which control the paradoxical phase of sleep are located in the pons, i.e., in the lateral part of the nucleus reticularis pontis oralis.[580] Pontile lesions involving the nucleus reticularis caudalis[293] abolish the muscle atonia of paradoxical sleep, and if the lesions include the locus coeruleus all indications of paradoxical sleep disappear.[294]

The thalamus also comes into consideration - in particular, its intralaminar nuclei. These "nonspecific" nuclei receive fibers from the reticular activating substance. Low-frequency electrical stimulation of these nuclei in various species produces a sleep state, many aspects of which are highly similar to those of natural sleep.[10,265,319,320] Thalamotomy in man (for the treatment of parkinsonism), in which intralaminar nuclei share in the damage not uncommonly results in hypersomnia, irreducible insomnia, or prolonged vigilance.[79] The conclusion reached was that the thalamus is clearly a participant in the regulation of the sleep-wakefulness rhythm and that the intralaminar nuclei may be instrumental in the implementation of sleep-inducing mechanisms.[79]

In regard to the cerebral cortex, there appear to be two opposing sets of influences on the cerebral cortex, one excitatory and concerned in wakefulness, and the other inhibitory and instrumental in the promotion of sleep. The evidence suggests that the cerebral cortex is not concerned in the initiation either of wakefulness or of sleep, and that the cortex may not be as important a component of the sleep-wakefulness mechanism as generally assumed, as it has been shown that periodicity in sleeping and waking persists after decortication.[43]

Hypersomnia in Man

The hypersomnic patient closely resembles a normally sleeping person, but the slumber is deeper and of longer duration. The patient can be aroused, and if the somnolence is not too deep he can answer questions and swallow food, but he quickly lapses again into sleep. The comatose patient cannot be awakened.

Disturbances in sleep-wakefulness were a conspicuous feature in the encephalitis occurring pandemically in 1917 and 1920. Some cases were characterized by prolonged somnolence and ophthalmoplegia, and others by agitation and hyperkinesias and, as a consequence, a shortened sleep period. Inversion of sleep, with hypersomnia during the day and wakefulness at night, was also noted during these pandemics.[87] The tegmentum of the midbrain was considered to be the chief site of damage in the somnolent patients, and the anterior hypothalamus in the patients who were agitated and had hyperkinesias.[555] In the St. Louis and Japanese virus encephalitides of more recent years, somnolence has been much less frequent. Sporadic cases characterized by hypersomnia in which the nature of the causative virus was not established have continued to crop out from time to time. In one such case almost unbroken sleep (at times associated with coma) lasted for five years; the caudal hypothalamus and rostral midbrain were found severely atrophied.[461] Other kinds of lesions resulting in hypersomnia have been observed. Multiple sclerotic plaques in the region of the midbrain can result in hypersomnia as an initial symptom of the disease.[99,257] Embolic abscess in the hypothalamus-midbrain junctional area, near the aqueduct, was, in one case, the basis of deep somnolence of two weeks' duration, and softening of embolic origin in the mesencephalic tegmentum and the medial thalamus was responsible for semiconsciousness, then unconsciousness, for eleven days, in another.[76]

Infarct in the region of the tegmentothalamic axis is another condition in which hypersomnia may occur, and in some instances an inversion of the sleep-waking rhythm has also been noted.[99,183] Infarct in a wider territory of the tegmentothalamic axis - from the intralaminar nuclei of the thalamus bilaterally downward to the retromamillary level of both sides (in the bed of the thalamoperforating arteries) also resulted in hypersomnia, which, after a week or so, was followed by apathy, then indifference, and other disturbances.[99] In rare instances intermittent hypersomnia has been noted as a leading symptom following infarction of the pons.[99] Hypersomnia is frequent in Wernicke's encephalopathy, characterized pathologically by damage in the walls of the third and fourth ventricles and aqueduct (see Chapter 22). Hypersomnia may also occur in a variety of conditions in which the sites of damage responsible for alterations in the sleep-waking rhythm are less clear, e.g., diabetes mellitus, uremia, head injury, meningitis, and African trypanosomiasis.

Hypersomnia occurring in association with a tumor is most common when the tumor involves the diencephalon or the midbrain, or both, sometimes in the absence of increased intracranial pressure. Attacks of somnolence even during animated conversation were noted in one patient in whom sarcomatous meningioma destroyed the infundibulum and tuber cinereum and infiltrated the mamillary bodies.[209] Somnolence, insomnia, or reversal of the sleep rhythm may result from severe damage of the hypothalamus by craniopharyngioma or adamantinoma,[99,142,216] and somnolence may occur in acromegalics.[116] Excessive sleep over a period of months (also other disorders, such as hemiplegia and extraocular muscle disorders) resulted from a cystic glioma of the midbrain (3 cm. in diameter) that extended into the pontile tegmentum; intracranial pressure was not

increased.[116] Tumor of the midbrain tectum which symptomatically resembled encephalitis lethargica,[73] or tumor involving the upper midbrain and thalamus,[472] or invasive pineal tumor,[116,215] may induce somnolence either through direct destruction of tissue or secondarily through a rise in intracranial pressure involving the brain stem. Even tumor of the pons and/or the medulla oblongata, including compression by cerebellar hemangioblastoma, can give rise initially to episodes of sleepiness, periodic deep dreamless sleep, or inversion of the sleep-waking rhythm.[143] Now and then, tumor of the thalamus may lead to hypersomnia (and other disturbances) if situated bilaterally and medially and not far from the hypothalamus.[99,141] The sleep-like state encountered in tumor of the cerebral cortex and white matter[140] is probably attributable to a compressive effect on the upper brain stem.

Treatment of hypersomnia should be directed toward eliminating the underlying cause. Drugs having the property of counteracting hypersomnia include caffeine with sodium benzoate (1.0 Gm. orally), ephedrine sulfate (50 mg. subcutaneously), and dextro-amphetamine sulfate (Benzedrine sulfate) (25 mg. orally, or 10 mg. subcutaneously).

Narcolepsy and Allied States

The term "narcolepsy" (narco, stupor; lepsy, seize) denotes attacks of irresistible sleep occurring during the daytime. This condition is not a form of epilepsy, nor can it be linked with any other convulsive disorder. For the attacks of loss of muscle tone, which are a feature in over half the cases of narcolepsy, the term "cataplexy" (to strike down) has been provided. Also in the framework of narcolepsy is the occurrence of paralysis experienced by the patient on awakening; it is called "sleep paralysis."

Idiopathic narcolepsy sets in fairly abruptly and can occur at any age, although most commonly in persons aged 10 to 30 years, of either sex. Gain in weight and polycythemia frequently precede the onset of narcolepsy.[515,576] The overpowering attacks of sleep that characterize narcolepsy occur suddenly and without warning. The sleep usually lasts a few minutes but may persist for an hour or longer. There may be only three or four attacks a day, or many attacks, even status narcolepticus. The daily number for a given person is, however, fairly constant. In depth, the slumber usually resembles natural sleep. Some persons have attacks while standing or while working. Or an attack may occur while the narcoleptic is walking, in which case he may bump into people and be accused of drunkeness. Diplopia may be complained of as a feature of an attack. The attacks may come on under conditions conducive to sleep; for instance, after meals or during monotonous work. Only occasionally are they initiated by emotional excitement. Attacks can sometimes be warded off by strenuous activity. The narcoleptic usually awakens spontaneously, refreshed and alert. Ordinarily he can be brought out of his slumber by the slightest stimulus; but at times the sleep may be so sound that he can be roused only by vigorous shaking. Sleep at night is like that of a normal person.

The EEG pattern during a narcoleptic attack differs from the normal by the rapidity with which paradoxical sleep is attained - after a minute of orthodox sleep (low voltage slow waves in the EEG), in contrast with the sleep of the normal person, in which orthodox sleep lasts an hour or so before paradoxical sleep sets in. The paradoxical sleep of the narcoleptic, which is accompanied by rapid eye movements, then passes over into orthodox sleep for a brief period, or he wakes up. If within an

hour another attack occurs, the sleep episode may be of the orthodox type; it is as though priority for paradoxical sleep has already been satisfied.[422] Dreaming occurs during the paradoxical sleep; the dreams are often a mixture of phantasy and reality.[422]

Cataplexy is characterized by attacks of sudden loss of motor power and muscle tonus, as the result of which the patient falls inertly to the ground. After a few seconds or minutes he is up again. Or only certain muscles or groups of muscles may be involved: an arm or a foot may be rendered powerless, both arms may briefly go limp, the jaw may sag. Or there may be status cataplecticus. Although occasionally monosymptomatic, cataplectic attacks usually occur in narcoleptics. The attacks customarily appear at the same time of life as the attacks of sleep but sometimes they set in a year or so later (or rarely slightly earlier). Narcoleptic and cataplectic attacks in the same patient occur at different times, though occasionally a cataplectic attack is followed by deep sleep. During an attack the patient is fully conscious. The attacks are almost invariably initiated by an emotional stimulus. Uproarious laughter is a common incitant; attacks thus induced (Lachschlag; geloplegia) can also occur in nonnarcoleptic persons. Or attacks may follow fear or sudden startle or in a surge of triumph over an opponent. During an attack the pulse may be slowed. Pupillary reaction to light usually remains normal. Tendon reflexes may be abolished. Cataplexy may be regarded as sleep localized to the somatomotor realm: the neural mechanisms concerned with posture and locomotion have, so to speak, fallen asleep. It is likely that the diencephalon is concerned, as cataplectic attacks are fairly common in colloid cyst of the third ventricle.[579]

Sleep paralysis - i.e., muscular paralysis occurring in association with the sleep process - may be monosymptomatic or occur in association

with narcolepsy or cataplexy, or both. The paralysis occurs as the patient is falling asleep or upon awakening. Paralysis on awakening, the commoner of the two, lasts a few seconds to several minutes, or even an hour or more, and vanishes either suddenly or gradually. Excitement does not seem to be a precipitating cause. The patient, although fully conscious, lies transfixed, unable to move a muscle, unable to talk (except in rare instances), and thus gives the appearance of being still asleep. He dreams, and the content of the dreams may be so terrifying that he struggles to escape, but on awakening he finds himself immobile. An attack can be culminated by touching the patient or by shaking him, but usually resolves spontaneously; loud noises are ineffectual. EEG recordings during such attacks reveal a low voltage pattern with frequent facial twitches interspersed with rapid eye movements.[422] Sleep paralysis may be viewed as the expression of a disorder in the central sleep-wake mechanism, whereby its component parts fail to react simultaneously, the component subserving wakefulness continuing to be active after that concerned in locomotion and posture has, so to speak, fallen asleep - or becoming active before that concerned in locomotion and posture have "awakened."

ETIOLOGY. Neither heredity nor disease in the patient's antecedents plays a significant role in the causation of narcolepsy, although a familial form has been reported. Some biochemical error may underlie idiopathic narcolepsy. This is made likely by the observation that the duration of the period of paradoxical sleep is doubled when the narcoleptic is given amino acid laevotryptophan (5 Gm.) prior to falling asleep, providing that he is not also receiving amphetamine.[180] Sleep paralysis is without a family history of a similar complaint except, occasionally, for relatives who have sleep paralysis or somnabulism.[474]

DIAGNOSIS. Narcolepsy and cataplexy are usually so distinctive that the diagnosis is in little doubt. Narcolepsy may be distinguished from petit mal by the reversibility of consciousness: in the former, by the ease with which the patient may be brought back to consciousness; in the latter, by the difficulty encountered in influencing the duration of the attack. Petit mal occurs chiefly in children; narcolepsy, in adolescents and adults. The slight clonic jerks occurring at a rapid rate in petit mal are unmistakable (see Chapter 24). Narcolepsy responds to amphetamine, petit mal to anticonvulsant drugs. Cataplexy is almost always precipitated by emotional excitement. It may be distinguished from petit mal and syncope by the preservation of consciousness.

PROGNOSIS. Attacks of narcolepsy and cataplexy usually occur over a period of years despite therapy, and the same is true for sleep paralysis. Prognosis is thus poor. There seems no recourse but for the patient and his family to get used to the situation.[515] Occasionally these disorders resolve spontaneously after a few months. Work performance is not materially impaired. The disorders do not in themselves reduce the life span, although occasionally an attack occurs under conditions that endanger life.

TREATMENT. The patient should not engage in an occupation in which he may endanger his own life or the lives of others, and should not drive an automobile or other vehicle. Dextro-amphetamine sulfate (Benzidrine sulfate) in a dose of 15 to 50 mg. per day has proved highly beneficial in the treatment of narcolepsy and cataplexy. Administration should be started in the morning. It is advisable to stop medication in the late afternoon so that the medication may not interfere with sleep. When amphetamine causes gastrointestinal disturbances, feelings of tension or anxiety, or cardiac palpitation with extrasystoles (or even a paranoid psychosis), Dexedrine

sulfate may be substituted, the maximal daily dose being 50 mg. If this drug cannot be tolerated, ephedrine sulfate may be tried (25 to 50 mg. three or four times per day). In some cases, narcolepsy has been controlled by desiccated thyroid, the initial dose of about 8 mg. being gradually increased to tolerance, as determined by the subjective response and the pulse rate. Methylphenidate (Ritalin), 60 to 80 mg. a day, has also been advocated.[576]

Symptomatic Narcolepsy

The Pickwickian syndrome[166,520] is one of the better known forms of symptomatic narcolepsy. The main characteristics are attacks of sleep during the daytime and gross obesity, which is consequent upon an enormous appetite. Respiration is impaired because of the obesity. Polycythemia also occurs. Other disturbances include cyanosis and right ventricular hypertrophy culminating in failure of the ventricle.

In Pickwickian patients the daytime episodes of sleep last 10 to 12 seconds and are accompanied by flattening of the EEG and slowing of the alpha rhythm as the first stage of orthodox sleep commences. Occasionally, the second stage of sleep is reached. The sleep is almost always associated with a rise in the threshold of the medullary response to carbon dioxide, which decreases ventilation;[295] however, in occasional Pickwickian patients episodes of sleep sometimes occur in the absence of carbon dioxide retention.[487] Arousal is spontaneous and abrupt, whereupon rapid, deep respiration occurs. Most of the night is spent in the second stage of orthodox sleep, preceded by frequent apneic periods in which the EEG is slowed and the amplitude of waves is increased.[295] Improvement in the condition sometimes follows reduction in weight.

Secondary narcolepsy is another category of symptomatic narcolepsy.

The term implies that recognizable brain damage has been incurred. The secondary form may develop as a sequela of epidemic encephalitis. In such cases the symptoms of cerebral involvement during the acute phase of the infection are usually mild. Those who come down with narcolepsy have in the meantime become obese, slowed in intellectual functioning, emotionally labile, and subject to a reversal of the day-night sleep pattern, so that they take night jobs.[422] Head injury has been cited as a precipitating cause of diurnal hypersomnia,[467,515] and pre-existing narcolepsy has been aggravated by cranial trauma. Narcolepsy has been noted in association with neoplasm involving the hypothalamus or rostral midbrain,[562] in cerebral arteriosclerosis, neurosyphilis, and subarachnoid hemorrhage. In multiple sclerosis, narcolepsy may be the initial symptom.[65] Narcolepsy is said to be intensified by menstruation and pregnancy. There are several reports of polycythemia vera in which narcolepsy was a complication. Blood lymphocytosis (to 50 percent) has been observed in narcolepsy, as has eosinophilia.

Hypnogogic Hallucinations, Nightmares, Somnambulism

Some narcoleptics and many non-narcoleptics experience hallucinations as they are falling asleep, i.e., they have "hypnogogic" hallucinations. More commonly, however, they occur upon awakening. The hallucinations, which occur during orthodox phases of sleep, are most frequently in the visual and acoustic realms, and are complex, vivid, and tend to be horrifying. During an attack the patient has the appearance of being awake.

True nightmares, by contrast, occur during the course of paradoxical sleep. They are "bad" dreams, commonly of a terrifying nature, in which the dreamer feels himself helpless to move. Nightmares differ from sleep paralysis in that the latter occurs upon awakening. Paradoxical sleep

prolonged beyond normal may tip the scales toward the initiation of nightmares, as suggested by results from the use of certain drugs.[180,424] Nightmares commonly occur upon withdrawal of certain drugs, such as barbiturates; also alcohol, in which addicts on the verge of delirium tremens, or already in this state, exhibit a relative excess of paradoxical sleep.[237,241]

Somnambulism represents an advanced stage of the motor unrest exhibited by those under severe life stress, notably after battle experiences during wartime. In the middle of the night a soldier may suddenly sit up in bed or jump out of bed to attack an imaginary enemy. When confronted, he may respond incoherently. Such episodes probably represent a state of disorientation, not a state of sleep.[422] Persons under some other kind of life stress may get out of bed and walk about in a fully coordinated fashion and, perform apparently purposive acts. He seems aware of his environment but is indifferent to it. He does not have the usual reaction to sense impressions, and afterwards he is unable to recall what he did during the somnambulistic period. Somnambulistic activity usually occurs during periods of orthodox sleep, most commonly in the third or fourth stages. EEG recordings reveal continuance of slow wave activity during the periods of motor activity, followed, in a minute or more, by low voltage theta, alpha and beta frequencies.[286,301,422] Somnambulism can be considered the converse to cataplexy in that higher centers are "asleep," while those concerned in locomotion and posture are "awake." The condition occasionally occurs in narcoleptics.

Insomnia

The inability to fall asleep in a reasonable time and to sleep for the accustomed seven or eight hours is a symptom that has many causes, the chief

of which follow:

Mental and emotional disturbances: worry in normal persons passing through some period of life stress and anxiety; psychoneurosis in general, hypomania, mania, toxic confusional states or delirium, manic-depressive states, anxiety neurosis. A patient with mania may sleep scarcely at all unless given heavy sedation. A depressed patient wakes early, and commonly paces to and fro about the house, ruminating, more than any other time of the day, on various morbid themes; his insomnia is genuine, as revealed in the EEG by flattened waves signifying lack of paradoxical sleep; in such persons disturbances in other autonomic functions are also recognizable.[234,423] Even greater sleep disturbances are noted in persons with anxiety neurosis, and they, too, are early risers.[376,380]

Abnormal bodily states: painful affections, nocturia, pruritus, fever, hunger, coldness, cough, hyperthyroidism, uremia.

Disturbance in conditioned stimuli: insomnia may be a habit formed during a period of sleeplessness, the causative factor of which has long ceased to operate. A change in the customary surroundings also may cause wakefulness. Nightworkers commonly have insomnia and complain of fatigue; they are eight times more prone to gastroduodenal ulcer and twice as apt to have cardiac infarction than control persons.[273]

Circulatory disturbances: arterial hypertension, chronic heart disease, heart failure, cerebral atherosclerosis.

Toxic influences: excessive use of coffee, tea, alcohol, ephedrine, barbiturates, amphetamine, cardiazole, theophylline, Dexedrine, desiccated thyroid. The use of barbiturates is followed by a prolongation of wakefulness, and when sleep does occur the proportion of the night spent in paradoxical sleep is significantly reduced.[423] The same is true

for amphetamine and related drugs[455] and for tranylcypromine[336] and meprobamate.[201] Withdrawal of barbituates or of amphetamine and related drugs is followed by a large increase above normal in the time spent in paradoxical sleep.[424,425]

Lesions of hypothalamic-midbrain region and in other parts of the neuraxis: viral encephalitis, cranial trauma, infarction, tumors.

TREATMENT. The simplest treatment consists of the elimination of stimulants (i.e., coffee or tea) during or after the evening meal. In elderly persons this may, however, serve to aggravate the insomnia, especially when coffee has, for years, been taken at bedtime to promote sleep. The usual simple methods used to induce sleep should be tried. Strophanthine eliminates the insomnia occurring in cardiac insufficiency.[273]

Special management, such as the use of hydrotherapy, re-education and psychotherapy, is usually required for psychogenic insomnia. Sedative drugs have a place not only in the treatment of the insomnia secondary to mental disorders, but also in the insomnia resulting from organic disease or pain. Withdrawal of barbiturates or of amphetamine and related drugs from the addicted may take as long as two months to resolve.[424,425]

DISORDERS OF TEMPERATURE REGULATION

The maintenance of body temperature within a narrow range requires that heat gained from metabolic activity and heat lost by means of other bodily mechanisms be balanced against prevailing environmental conditions.

The human body operates at an internal temperature of approximately 98.6°F (37°C), while the skin temperature is 92°F (33.5°C). Heat gained and heat lost by the body depend on a number of factors. Much heat is gained through metabolic activity ("metabolic heat"); for example, hard exercise by athletes will raise the rectal temperature to 104°F (40°C).[164]

In a resting body with zero heat exchange the storage of metabolic heat would raise the body temperature about 4°F (2.5°C) per hour, and if the subject were walking, the temperature increase in the body would be two or three times this value.[482] Much heat is also gained through radiations from the sun. Its amount is the same regardless of the air temperature. At an environmental temperature greater than 92°F the body also gains heat through convection, i.e., by air molecules that carry heat to the skin. Heat conduction as a factor in increasing heat load refers to the passage of heat through the body, from one molecule to another, as from heated clothing. With an environmental temperature higher than 92°F, body heat is lost almost solely through evaporation, both through insensible perspiration (drying of tissues through the skin) and through sweating, the latter of which does not commence until there is a need for cooling. Soldiers marching in the hot desert vaporize 1 to 1-1/2 liters per hour. By evaporating, the sweat cools the skin and in turn the blood bringing heat to the body surface, such that 585 calories are taken care of by each liter vaporized.[164] Adequate heat can thus be dissipated from the body surface if the atmospheric humidity is not excessive and if the velocity of the air current is sufficient to carry adequate amounts of heat away from the body. In regard to the factor of humidity, a man carrying out hard work (425 kg. cal/hour) cannot remain in thermal equilibrium at a relative humidity greater than 55 percent if the air temperature is 90°F (32°C), because the air will not absorb enough moisture from his body surface to take up the heat load. In summary, in a hot environment heat is gained through metabolism, radiation, convection, and conduction, and lost through evaporation.

In temperate climates (i.e., at temperatures less than 92°F), heat

is also gained through metabolism and solar radiation. Since heat flow is from the body to the environment, more means are available for heat loss than under hot climatic conditions. An average man carrying out light work dissipates about 3000 calories daily, of which approximately 65 percent are dissipated by radiation, convection, and conduction from the body surface into the atmosphere, and about 25 percent by evaporation of water from the skin and lung surfaces.

As heat stress on the body increases, whether under hot or temperate climatic conditions, a number of changes take place. Sweating removes salt and water from the body. When sweat evaporates from the skin, the latent heat of vaporization is removed from the skin and superficial tissues. The required increase in conductance when heat from the interior of the body needs to be removed is largely achieved by an increase in peripheral blood flow and distention of the superficial vessels. In the absence of a corresponding increase in blood volume the interior of the body is robbed of blood, leaving the heart with less blood to work on. This is made up for by a compensating increase in heart rate, to maintain circulation. As long as every step in the process is within the capacity of the organism, and the heat load is not too great, thermal balance can be maintained.

On rapid change from a warm to a cold environment, the mechanisms of heat conservation come into play first; if these are inadequate, then mechanisms of heat production are marshalled. Body heat is conserved chiefly by a shift in body water from the skin to the internal organs. The concomitant decrease in plasma volume also protects the body from heat loss by offering less heat to surface regions. These changes are brought about largely through the activity of the autonomic nervous system.

An increase in heat production is accomplished by greater food intake and by increased physical activity. When, despite these reactions, the body temperature tends to fall, other mechanisms of heat production become activated. The chief of these are muscle tenseness and shivering, the latter appearing when the temperature of the body core falls a degree or two. The production of body heat depends largely on the metabolic activity of muscle cells. In extreme shivering the muscular work entailed may increase the oxygen consumption as much as five-fold. When exposure to cold is sufficiently prolonged and severe, shivering ceases [at around 86°F (30°C) central core temperature], muscles lose their tenseness, body temperature falls further, and muscular paralysis sets in. Death usually occurs when the rectal temperature falls to about 74°F (23°C) but survival after the rectal temperature has fallen to 68°F (20°C) has been reported.

Experimental Studies

The hypothalamus contains a dual temperature regulating system, heat dissipation being largely a function of its rostral part, and heat conservation and heat production largely a function of its caudolateral part, as has been demonstrated by various means. Lesions placed rostrally impair an animal's capacity to eliminate rising body heat.[55,450,533] Heating of blood reaching the rostral hypothalamus results in sweating and other manifestations of heat dissipation.[248,533] Moreover, electrical stimulation in this region in goats with indwelling electrodes induced polypneic panting, cutaneous vasodilatation, and cessation or reduction of physiologically induced shivering, and when stimulation was carried out in a cold environment the rectal temperature fell 1.8 to 9°F (1 to 5°C).[27] Even when the rectal temperature was lowered to 18°F through prolonged stimulation electrical stimulation of the preoptic area was still capable of

Fig. 27-16

inducing some degree of polypnea[29] (Fig. 27-16). The rostral hypothalamus is also concerned in heat production, as brought out in the monkey with the use of biothermodes inserted into the preoptic region. Cooling produced coordinated behavioral, autonomic, and neuroendocrine responses. These included peripheral cutaneous vasoconstriction, piloerection, increased motor activity, and shivering, and elevation of arterial blood temperature and arterial blood pressure. Vasopressin release was inhibited, leading to diuresis with increased free water clearance, increased plasma osmolality, and decreased urine osmolality.[259]

By contrast, the caudolateral part of the hypothalamus is concerned largely in heat conservation and production. Damage inflicted in this region results in prolonged hypothermia, incapacity to react to cold (e.g., by shivering), diuresis, hemoconcentration, and failure of the blood sugar level to increase in response to cold, as has been shown in dogs, cats, and monkeys.[304] Relative poikilothermia occasionally results from damage of the caudolateral hypothalamus.[450] Body temperature remaining 9 to 18°F (7.5 to 15°C) warmer than the environment for as long as ten weeks has been induced in cats by injuring the medial hypothalamus, but the size of the lesion, not its position, was probably the chief factor in the disturbance of temperature regulation.[530]

The main determinant of the body response to a change in environmental temperature is the temperature of the blood reaching the hypothalamus. The preoptic region of the hypothalamus contains thermosensitve neurons, called <u>thermodetectors</u>, capable of converting thermal energy into electrical energy[556] (Fig.27-17). Some of the thermodetectors are heat sensitive units.[251,394,398,556] These thermodetector neurons serve in thermoregulation largely through biochemical means. Evidence has suggested

Fig. 27-17

that the biogenic amine, serotonin, is selectively released in the preoptic region for the activation of a neural pathway passing to the posterior hypothalamic heat production center when thermogenesis is needed.[394] Another biogenic ammine, noradrenaline, is also involved. On the one hand, it has been concluded that noradrenaline liberated in the preoptic area blocks the hyperthermic action of serotonin and thus deactivates the posterior hypothalamic center, allowing heat loss to occur through some other neural mechanism when cooling is required.[394] Another view is that, in response to warm or cold, increased turnover of noradrenaline occurs at nerve endings generally in the hypothalamus, not specifically in the preoptic region.[500] A chemically mediated heat loss pathway has not been identified in the hypothalamus.[185,394-396]

The caudolateral part of the hypothalamus, by contrast, is "temperature-blind."[62-64] It is the site of origin of a number of systems capable of initiating or inhibiting vasomotor, sudomotor, respiratory, and somamotor activity,[62,64,282] and therein lies its importance in temperature regulation. Evidence supports the view that cells in this caudolateral regulatory center have a predetermined set-point of 98.6°F (37°C). By virtue of this quality they have the capacity to control the magnitude of heat production and heat loss. Maintenance of the set-point and mobilization of reactions to defend this set-point are achieved through effector signals coming from the anterior hypothalamus.[63,113] Effector signals come also from the septal region and the subthalamus through which shivering is initiated or facilitated.[25,27,54,248,282,304] Impulses coming from the periphery are encoded by cutaneous and deeper-lying temperature receptors and then are sent via ascending pathways to the caudolateral hypothalamic center, affecting its activity.[63,277,542]

The point was made in the foregoing that the anterior hypothalamus serves only to regulate the efferent heat production pathway. The question thus arises as to the means by which peripheral heat loss systems are activated. Acetylcholine-like substances micro-injected into the transitional region between hypothalamus and midbrain have given rise to a profound and often long-lasting hypothermia, from which it has been thought that one set of efferent neurons in this general region mediates heat loss, while another set of efferent neurons mediates heat production.[396]

The main pathway through which impulses concerned both in heat dissipation and in heat conservation (and production) are conveyed takes its course through the caudolateral hypothalamus, midbrain and pontile tegmentum, reticular formation of the medulla oblongata, and lateral columns of the spinal cord, then by way of sympathetic fibers to cutaneous vessels and sweat glands, and through somatic motor fibers to muscles. Hormonal responses to temperature change are mediated via hypothalamo-hypophysial systems. Inhibition of vasopressin release in response to cold and increase in response to heat have already been mentioned. The thyroid gland also responds rapidly to cold, as indicated by thyroid enlargement and by an increase in thyroxin secretion[273a] and in ^{131}I uptake. The hypertrophy of the thyroid that follows exposure to cold no longer occurs after section of the hypophysial stalk.[557] Under conditions of cold, an increased amount of TSH has been found in the tuberal region,[72] suggesting that this hormone may influence hypothalamic neural mechanisms concerned in energy expenditure. Moreover, under conditions of cold, adrenal corticoid excretion is increased,[160] but the relevance of this response to temperature regulation remains uncertain.[118]

Heat Illness

Heat illness is divisible into four forms: heat cramps, heat exhaustion, borderline heat hyperpyrexia, and heat stroke. Although each may justifiably be regarded as a separate clinical entity, one form may overlap with another.

Heat cramps is characterized by painful contractions of skeletal muscles and a sensation of nausea. The condition is brought on by loss of sodium chloride in the sweat. The cramps may be due to relative increase in water content in muscles.

Heat exhaustion may be subdivided into two types: mild, as manifested by exercise-induced collapse, syncope, and acute asthenia, and associated with mild water deficiency and usually with salt deficiency as well; and severe, related mainly to salt deficiency, with heat cramps in 60 percent of cases.[337] Mild heat exhaustion is also referred to as heat collapse, and heat syncope. It is attributed to extensive vasodilatation by the direct action of heat, with resulting pooling of the blood in the lower half of the body, postural hypotension, hence inadequacy in the supply of blood to the brain. The severe form is referred to as salt-deficiency heat exhaustion. In this form, headache is usually complained of. Nausea and vomiting commonly occur. Weakness, pallor, and giddiness are also characteristic. Persons with heat exhaustion sweat profusely. The body temperature may be normal, subnormal, or slightly elevated. The symptomatology resembles that of shock, with failure of the peripheral circulation together with cardiac embarrassment (oligemic shock). In rare instances, heat exhaustion is manifested by severe shock which proves fatal.[368]

Borderline heat hyperpyrexia refers to a condition in which the body

temperature lies between 103° and 106°F (39.5° and 41°C) and in which anhidrosis and most of the disturbances listed under severe heat exhaustion are noted.[331] A synonym is anhidrotic heat exhaustion.[337] The patient is conscious and rational, which distinguishes this condition from heat stroke.

Heat stroke carries a mortality rate as high as 50 percent. The condition usually comes on with dramatic suddenness (hence "stroke") but is commonly ushered in by premonitory symptoms or occurs insidiously over a period lasting several days. Its distinguishing features are defective sweating, hot and dry skin, rapid pulse, rapid respiration, signs of circulatory collapse, delirium or coma, convulsive seizures, and a body temperature of 106°F (41°C) or higher, although in heat stroke the temperature may be somewhat lower than 106°F.[337] An acute mental disorder is occasionally the presenting disturbance even in the absence of severe hyperpyrexia.[52,479,553] Hematuria is commonly noted, and there may be petechiae in the skin and mucous membranes.

Among the factors predisposing to heat stroke are lack of acclimatization and adverse environmental conditions. Exposure to unaccustomed heat causes vasodilatation in skin and muscles without an immediate corresponding increase in blood volume, hence the pooling of blood in superficial dilated vessels and resulting cardiovascular instability. During the process of acclimatization neuroendocrine homeostatic mechanisms bring about various adjustments: the cardiovascular system increases in efficiency, sweating starts more readily, the ability to secrete sweat increases, salt loss in sweat decreases, and the rise in rectal temperature following a given work load decreases. Full acclimatization may be achieved in about a week.[337] Predisposing environmental conditions needing to be taken

into account are temperature, relative humidity, and degree of physical exertion. Other predisposing factors include impaired general health, adiposity, prior fatigue, consumption of alcohol, and reduced cardiac and renal function.[35,188,229,465] Heat stroke may develop, and prove fatal, in healthy young soldiers undergoing moderate exertion under environmental conditions ranging from 120°F (49°C) at 8 percent relative humidity to about 85°F (28°C) at 65 percent relative humidity.[482]

As to the pathogenesis of heat stroke, information is available on certain aspects. Cessation of sweating is commonly an initial sign of impending heat stroke, although considered in context the cessation occurs after the body temperature has risen considerably and the pulse rate has become elevated in response to the heat stress. The cessation has commonly been attributed to failure of the secretory mechanism of the glands (i.e., "sweat gland fatigue"),[543] through the operation, possibly, of serum potassium depletion[111] or from elevated venous pressure.[225] The fact that cessation of sweating occurs at the same time all over the body has, on the other hand, suggested failure of a central mechanism, presumably a hypothalamic mechanism.[329] "Exhaustion" of the sweat apparatus from peripheral causes can apparently be ruled out on the basis that sweating is rapidly restored when the subject returns to cool air. Body heat per se appears not to be a significant factor in sweat cessation, for when sweating is restored on return to cool air, the rectal temperature remains at its previous height or rises still further.[329] Prolonged dehydration, by contrast, progressively reduces thermal sweating,[338] though there are dissenters on this point.

Elevation of body temperature per se would seem not to be the most significant factor in the causation of heat stroke, for persons in good

condition undergoing fever therapy can withstand 107.6°F (42°C) for periods of eight to ten hours without deleterious effect, and patients can survive a body temperature as high as 113°F (45°C).[164] A number of bodily mechanisms are involved, of which reduced capacity to sweat is one of the most evident. Another is rise in heart rate, which may be a better measure of heat stress than rectal temperature, for in persons exercising in a warm room the heart rate may approach 180 per minute with little rise in body temperature. Apparently the peripheral vasodilatation, which accompanies increased heat conductance, can drain so much blood into the capillaries near the body surface that there is insufficient venous return of blood to the heart, as a consequence of which the heart muscle itself becomes exhausted through failure to receive adequate blood supply. It would seem, then, that heat stroke is initiated by the continuance of conditions that make thermal equilibrium impossible, and that the cessation of sweating and certain other disturbances that occur are the outcome of an incapacity of the central nervous system to meet the unremitting requirement for greater and greater heat elimination.

Pathological processes occurring in the course of heat stroke vary in nature and intensity from case to case. Hypernatremia precedes or accompanies heat stroke in a fair percentage of cases.[35,52] Potassium content in various tissues undergoes alterations following exposure to heat. In dogs subjected to severe heat stress an increase in K content occurred in heart and skeletal muscle, and a decrease in liver and jejunum with increase in extracellular K, though the blood serum content of K was not ascertained.[522] In earlier stages of fatal heat stroke there is frequently a depletion of serum K (to less than 4 mEq. per

liter),[52,368,553] with a lowering of total body K.[111] The decrease is due in part to the increased loss of K in the urine and sweat. It has been suggested that K reduction might increase susceptibility to heat stroke,[111] and it has also been suggested that exercise in persons with reduced K may lead to disruption of skeletal muscle.[553] In cases in which heat stroke is well underway the K level in the serum is increased, of a magnitude not encountered in acute renal failure alone, suggesting that exposure to heat significantly accelerates the movement of potassium out of cells. The hyperkalemia may be due to a combination of factors: (1) cellular destruction resulting from prolonged hyperthermia and severe tissue hypoxia secondary to shock, (2) hypernatremia with consequent movement of potassium extracellularly, (3) destruction of sequestered heat-damaged erythrocytes, and (4) the extracellular movement of potassium in response to severe decompensated metabolic acidosis.[52] Death in such cases may result from fulminating myocardial potassium intoxication.[52]

In fatal heat stroke, hemorrhages have been found in many organs, including the brain. Necrosis of megakaryocytes in the bone marrow, with marked fall in the platelet count, is one of the causative factors.[168,368] Another is endothelial cell damage leading to hemorrhages and disseminated intravascular coagulation, as observed under the electron microscope; the acute coagulopathy was considered a possible precipitating cause of heat stroke.[513] Renal failure occurs in from 2 to 9 percent of cases of heat stroke, and is frequently completely reversible.[553] Hypotension greatly increases the risk of this complication. Exertion-induced rhabdomyolysis and myoglobinuria are frequent accompaniments.[553] Lower nephron nephrosis is observed in occasional fatal cases.[35,368] Sites

of brain damage in fatal heat stroke include cerebellar cortex, cerebral cortex, striatum, and thalamus.[368] Neuronal changes in certain hypothalamic nuclei have also been described.[388]

Sequelae are frequent in persons who recover from severe heat illness. Such persons are usually intolerant of heat; they become extremely uncomfortable when under heat stress. There may be subtler changes, such as emotional instability and irritability, childishness, clumsy articulation, and lowered tolerance to alcohol.[377,529] Permanent anhidrosis has occasionally been demonstrated. This was noted in a man with paratyphoid fever whose temperature had remained elevated for about three months [peak, 106°F (41.5°C)]. Skin biopsies revealed no pathological changes in sweat glands.[199] Another instance concerned a ship's engineer who for months had worked overtime in an excessively hot engine room which had a high relative humidity. Cessation of sweating with hyperthermia and partial circulatory collapse occurred on one occasion, and months later he had such intolerance to heat that exposure to a warm climate brought on total incapacitation. Tests for sweating revealed widespread anhidrosis (author's observation). For cases of this kind irreparable damage of the heat dissipating mechanism in the hypothalamus is postulated on the basis. Other sequelae include a cerebellar syndrome (incoordination, ataxia, dysmetria); the syndrome develops either immediately following recovery from heat stroke or after a delay of some weeks.[202,529] Neurological sequellae of heat stroke in Kuwait, Arabia, included mental disorders, cerebellar ataxia, hemiplegia, and flaccid quadriplegia.[479] Peripheral neuropathy was one of the most prominent findings in a prisoner who had suffered heat stroke, as manifested by muscle wasting in the hand and lower limbs, abnormal electromyogram,

and lack of nerve conduction in the lower limbs.[377]

TREATMENT. Heat cramps are prevented or alleviated through generous supplementation of the diet with salt. In persons with mild heat exhaustion the giving of salt by mouth may suffice. However, in the average case physiological saline should be given intravenously. Rapid recovery usually follows this form of treatment; should little response occur it is probable that the subject is a candidate for heat stroke. In heat stroke the two immediate goals in management are to lower the body temperature and to reconstitute the blood volume. Lowering the body temperature is accomplished by packing the patient in ice, fanning, and massage (to promote vasodilation) until the temperature falls to about 101°F (38°C). It is important that shivering be controlled. For this purpose and to tranquillize, small doses of chlorpromazine (Thorazine) or diazepan (Valium) may be given (i.v.). Colloid or crystalloid fluids are administered (i.v.) while central venous pressure and urinary output are monitored, but care in giving fluids should be exercised, as severe dehydration seldom occurs in heat stroke. The solutions are given in sufficient amount to maintain the venous pressure between 10 and 15 cm. H_2O.[168] Oxygen is given to combat tissue hypoxia and acidosis. Seizures can be controlled by administering Valium (i.v.) in small doses.

Base deficit should be calculated and corrected with sodium bicarbonate. Serum potassium and pH determinations should also be made as soon as possible. One should be on the alert for a dangerously low potassium level, which may develop particularly after partial respiratory compensation of the metabolic acidosis and after administration of sodium bicarbonate. The initial hypokalemia enhances renal damage, and the ensuing renal failure may lead to hyperkalemia; hence potassium should be

administered judicially.

For high-output cardiac failure and associated pulmonary edema digitalization has been recommended but should be used with great caution because of the threat of digitalis intoxication from poor renal excretion of the digitalis.[225,229] Adrenal steroids have disadvantages but may be used when the patient is in shock and does not respond to other measures.[229] This should, however, be done advisedly, for steroids tend to reduce the plasma fibrinogen level, thus aggravating existing hypofibrinogenemia.[431]

Hemorrhage and intravascular coagulation are treated simultaneously. Heparin should be given in adequate dosage (2 mg./kg every six hours). Immediately after the initial dose of heparin, epsilon-amino-caproic acid (a potent synthethic amino acid which is a competitive inhibitor of plasminogen activation) is given slowly in a dose of 6 Gm. (i.v.), followed by 0.5 Gm. every hour, to inhibit the fibrinolytic mechanism. If hypofibrinogenemia is severe (less than 100 mg. percent), 4 Gm. of fibrinogen are administered (i.v.). Other conditions that might occur, such as acute renal failure, also need to be combatted.[229,553] Such failure comes into consideration only if it persists after complete resuscitation from shock.

Fever

There is ample evidence to support the view that a pyrogen is released from leukocytes during fever of infectious origin and that this leukocyte pyrogen is the agent that alters the functioning of the thermoregulatory system. In the febrile subject, qualitatively normal thermoregulatory responses to low and high ambient temperatures are preserved but they vary about a new, elevated set-point. Pyrogens appear to act in a region identical with or close to the thermoreceptor area, i.e., in the preoptic and anterior regions of the hypothalamus. Leukocyte or

bacterial pyrogen injected into this region induces fever at doses ineffective by systemic injection.[113] On the other hand, complete ablation of the posterior hypothalamus (in dogs) abolishes the fever response to pyrogens.[544] Mechanisms proposed in an effort to provide an explanation are: (1) that pyrogens depress the excitability of the thermoreceptor neurons to local heat, and in this way alter the set-point mechanism situated in the caudolateral hypothalamus, and (2) that when a pyrogen impinges on a "serotonin cell" in the preoptic area, the cell releases serotonin, triggering the efferent pathway for heat production.[554] Considering the increase in basal metabolism in the presence of fever, an increase in appetite might be expected. Anorexia, however, occurs. It has been suggested that this anorexia of fever may be the outcome of thermoreceptor reflex action on the food intake mechanism analogous to the change occurring in the temperature set-point.[456]

Fulminant Hyperthermia During Anesthesia and Surgery

Rapid increase in body temperature occasionally occurs in apparently healthy persons during the administration of anesthetics for non-critical surgical procedures, and usually proves fatal. The incidence has been highest in children.[81] The anesthetic drugs used have included nitrous oxide, thiopental sodium, succinylcholine, and halothane.[81] Tachycardia and pulmonary edema occur and the temperature climbs well over 106°F (41°C). There appears to be a deficit in the ability to hyperventilate in the face of increased tissue oxygen requirements. Paralysis usually develops, but a sizable proportion of cases are characterized by suddenly occurring and sustained generalized muscle tenseness or rigidity, even hyperrigidity passing into rigor mortis. Serum potassium level is raised in association with muscle rigidity, and there may also

be hemo- or myoglobinuria. Cardiac arrest usually precedes death.[81,473,525] Normally, anesthetics are an effective means of lowering body temperature. This reduction may be brought about by the action of the anesthetic on catecholamine-containing cells in the caudolateral hypothalamus, thus activating heat-loss systems.[394] Conceivably, the rise in temperature during anesthetization may be due to failure of a mechanism such as this one, whereby the "thermostat" in the caudolateral hypothalamus is reset in an unopposed manner. Through analogy it has been suggested that the muscle rigidity is more likely to be of peripheral than of central origin, one, because patients with trauma-induced disturbances in hypothalamic temperature regulation do not display the extreme metabolic acidosis and hyperkalemia observed in the condition under discussion, and, two, while patients with heat stroke do manifest metabolic acidosis and potassium intoxication, their muscles are usually found to be flaccid.[81]

Underlying or inciting causes are multiple. A constitutional factor may be involved in some instances, as a patient having a hyperthermic reaction with rigidity while under anesthesia may exhibit the same disturbances on reanesthetization; further, familial instances of death on the operating table are known.[81] Atropine given in excess, leading to temperature elevation as high as 109°F (43°C), has been traced as the cause in some cases. Introduction of pyrogen in intravenously administered fluids should also be taken into consideration when hyperthermia occurs. Preexistent musculo-skeletal disease has been noted in some instances, but whether there is any connection with the hyperthermia remains conjectural. Autopsy studies have been unrevealing except for evidence of hypoxia.[81]

Treatment is directed toward immediate reduction in body temperature, along the lines indicated for heat stroke. If the patient is on the operating table with the abdominal cavity open, a reduction in temperature can be achieved by instilling, into the cavity, cold Ringer's lactate or saline solution. To combat muscle rigidity, tubocurarine chloride is recommended. Withdrawal of blood through a centrally-directed venous catheter will prevent overloading of the cardiovascular system. Inhalation of 100 percent oxygen is indicated as an aid in the elimination of carbon dioxide. Acidosis is combatted by giving sodium bicarbonate (i.v.), the level controlled by arterial blood gas sampling. Dehydration and electrolyte imbalance should be corrected, and controlled through appropriate laboratory determinations.[473,525]

Temperature Disturbances From Lesions of the Central Nervous System

Hyperthermia and, less commonly, hypothermia, or even relative poikilothermia, may result from lesions of the hypothalamus, brain stem, or the cervical part of the spinal cord. The direction which the temperature deviation takes depends on the degree of the ambient temperature and in some measure on the site of the lesion. Deviations in body temperature are greatest when tissue damage is acute. Operations in the region of the third ventricle are not uncommonly complicated by severe hyperthermia. Under such conditions the body temperature begins to rise within twelve hours after operation. In some instances tachycardia precedes the elevation of temperature and in a day or two the patient may die from heart failure. Respiratory rate often ranges between 40 and 50. The limbs are cold and the trunk relatively warm. Unconsciousness is the rule.[177] By contrast, in some patients in whom hyperthermia results from operative manipulation of the hypothalamus, cardiac and respiratory rates remain

normal and consciousness is retained.[195] The hyperthermia is resistant to antipyretic drugs, but usually responds to external cooling measures.

Hyperthermia has occasionally been found associated with acute ischemic damage of the hypothalamus.[581] Sharply delimited softening in the preoptic region bilaterally, extending from the region of the optic chiasm to the anterior commissure was found in one case of this kind following removal of a subdural hematoma ten hours previously.[53] In another case, in which the hypothalamus suffered widespread damage bilaterally as the result of head trauma, there were bouts of hyperthermia for the first two or three days, after which temperature control was regained and maintained until death on the twenty-first day.[70a] Hyperthermia with unilateral hyperhidrosis has been observed in association with a chronic inflammatory process limited to the hypothalamus,[87] and hyperthermia in the presence of infarction of the midbrain.

When the hypothalamus is slowly destroyed, sometimes in its entirety, as by craniopharyngioma, no changes in body temperature may be noticeable. On the other hand, permanent disturbances in body temperature, usually an elevation, have been observed in the presence of tumors of the hypothalamus, including those medially situated.[581] One case of supraseller angioma was characterized by pronounced hypothermia, anhidrosis, fall in basal metabolic rate, diabetes insipidus, increased glucose tolerance, obesity, somnolence, and hypogonadism; except for the preoptic nuclei, virtually all the hypothalamic nuclei had been destroyed.[145] Profound hypothermia, lethargy, probable fall in basal metabolism, and an elevation of blood magnesium, mimicking a state of hibernation, have been observed in an infant with a hemangioendothelioma that destroyed much of the infundibular stalk, the caudal part of the infundibulum, and most of the ventromedial nucleus bilaterally.[538] Anhidrosis of hypothalamic origin may also occur, especially

when the damage is widespread and severe.

Relative poikilothermia in the presence of a hypothalamic tumor is rare. Such a disturbance was noted in a newborn infant with an infiltrating neuroblastoma that had "destroyed most of the hypothalamic nuclei," leaving only the supraoptic nuclei intact.[139,144]

HYPOTHALAMUS AND THE GASTROINTESTINAL TRACT

Gastric secretory activity in preparation for the reception of food is under the influence of the hypothalamus. The hypothalamus also plays a role in gastrointestinal motility, although under resting conditions the motility is virtually independent of impulses from the central nervous system.[174] Superimposed on the hypothalamus in its influence on gastric secretion and gastrointestinal motility are the limbic lobe and the neocerebrum. On the afferent side, vagal projections originating from distention receptors in the wall of the stomach have been traced to components of the limbic lobe: the orbitofrontal cortex[37] and the amygdala.[152] Splanchnic representation has also been identified in the somatosensory cortex,[161] more properly called the somatoviscerosensory cortex.[196] Also on the afferent side are humoral factors, for example, plasma glucose, to which hypothalamic glucoreceptors respond. Operating on the efferent side are the sympathetic and parasympathetic systems and the hypothalamo-pituitary-adrenal cortical system.

Mechanisms Influencing Gastric Secretory Activity and Gastrointestinal Motility

Electrical stimulation of the rostral hypothalamus (in monkeys) induces a prompt increase in gastric hydrochloric acid (indicated by a fall in pH), the secretion reaching a maximum in about one hour. The efferent pathway is by way of the vagus nerve, inasmuch as vagotomy prevents the response.[205]

By contrast, stimulation of the "sympathetic" area of the hypothalamus - the tuberal and caudolateral hypothalamic regions - induces gastric acid secretion after some delay, with maximal secretion in about three hours after stimulation. This secretory response is not influenced by vagotomy. Prior bilateral adrenalectomy prevents the response. The assumption is that the effect is humorally induced and is mediated by the anterior pituitary through its action on the adrenal cortex.[439] Similar results have been obtained (in monkeys) following continuous electrical stimulation of the hypothalamus up to 4 weeks. Increased sensitivity to submaximal doses of histamine was observed, as manifested by increased acid response to submaximal stimulation without any change in the fasting acid output or maximal histamine response. The responsive areas in the hypothalamus were situated anteriorly and medially, close to the ventricle. After cessation of stimulation the acid response reverted to normal.[246]

The cerebral neocortex is also concerned in the functions under discussion. Some splanchnic afferents, in their ascending course, make connections with the reticular substance, and through this medium they have the capacity to exert an excitatory state in the cerebral cortex.[207] On the efferent side, "splanchnic" fibers from much of the cortex, projecting to the brain stem,[204] may also exert their influence through the reticular substance. Gastrointestinal motility responses obtained from much of the cortex may thus be of a nonspecific character.[174] Specific reactions are also involved. Stimulation and ablation studies have shown that the cerebral cortex influences gastric and intestinal motility. Electrical stimulation of Brodmann's area 6 induces inhibition of peristalsis, and ablation an increase in peristalsis and, sometimes, fatal intussusception. On stimulation of area 8 in monkeys intussusception

occurred regularly, as did also an increase in the volume of gastric secretion and an increase in the concentration of pepsin and free hydrochloric acid.[565] Electrical stimulation of the human cerebral cortex has occasionally induced abdominal sensations, and then only from the insular region;[434] in one patient motility of the gastrointestinal tract was increased when the insula was removed.[433]

Considering, now, the limbic lobe, electrical stimulation of the orbitofrontal cortex inhibits (or occasionally increases) gastric motility, while ablations result in prolonged reduction of gastric acidity, but in no apparent alteration in motility.[37] Pronounced motility changes have also been produced by stimulating the amygdala.[152] The effects on gastric acid secretion produced by lesions in certain parts of the hypothalamus have been attributed in part to severance of connections between the hypothalamus and limbic lobe as well as the cerebral neocortex. Lesions made in the anterolateral hypothalamic region bilaterally (in dogs) have resulted in a statistically significant increase in basal acid secretion, whereas insulin-induced gastric secretion was inhibited for as long as three months. The increase in basal acid secretion was interpreted as due to interruption of fibers of the fornix and medial forebrain bundle (bilaterally) coming into the hypothalamus from the limbic lobe and the frontal neocortex, fibers which normally exert a tonic, inhibitory effect on basal gastric secretion. The inhibition of insulin-induced gastric secretion was thought to be due to alterations in conduction in diffuse descending connections from the lateral hypothalamus extending caudalward in the lateral tegmentum to the lower brain stem autonomic (vagal) centers.[138]

Another example that might be cited has to do with bile secretion.

Electrical stimulation of the posterior hypothalamus (in cats) causes a significant increase in flow from the isolated common bile duct, together with a significant increase in average potassium concentration in bile samples. However, when electrical stimuli were applied to the anterior hypothalamus or the dorsal hippocampus prior to posterior hypothalamic stimulation, the expected increase in bile flow and potassium concentration did not occur. When the dorsal hippocampus was alone stimulated, a significant increase in bile flow also occurred. Presumably, then, the hippocampus inhibits the posterior hypothalamic secretory effect, and it may also, through a different neural mechanism, cause an increase in bile flow.[70]

Gastrointestinal Hemorrhage and Ulceration

Overactivity of the hypothalamic mechanism under discussion results in gastric injury. Prolonged hypothalamic stimulation (two to four times daily for four to ten weeks, in monkeys) through implanted electrodes often results in hemorrhage and ulceration in the gastric mucosa.[206] Mucosal ulceration has also been produced (in dogs) by electrically stimulating the tuberal region, with the vagi intact, or by stimulating the vagi themselves. The sympathetic system is also concerned. Prior sympathectomy does not prevent the ulceration that occurs after damage of the tuberal region, but it does prevent the occurrence of mucosal hemorrhages.[56,303] Considered in the light of these results, as well as the results of others,[126] it appears that mucosal ulceration results from vagal overactivity, through which the musculature of the gastrointestinal tract undergoes contraction, leading to ischemia and, as a consequence, hemorrhagic infarction, then ulcer formation.

Lesions situated almost anywhere from the rostral hypothalamus to the

region of the vagal nuclei in the medulla oblongata may give rise to acute hemorrhagic erosions of the gastric mucosa, extensive ulceration of the lower esophagus and stomach, and acute perforations of the esophagus, stomach, and duodenum.[126,136] Such lesions are most apt to occur following damage to or pressure on the hypothalamus, particularly its tuberal region; in order to produce these effects in experimental animals the tuberal lesions must, however, be relatively large.[492] In man, too, gastrointestinal lesions of this kind are most commonly met with in the presence of lesions of the hypothalamus and other cerebral sites.[165,419] In dogs subjected to postinfundibular injury, submucosal gastroduodenal hemorrhages are succeeded rapidly by erosion and ulceration and, occasionally, after considerable time lapse, by the development of chronic gastric ulcers.[96] In man the spinal cord is not immune, for gastrointestinal bleeding following acute cervical cord injury has been noted in as high a proportion of cases as 20 percent.[435] The mucosal erosions and ulcerations that have occurred under many of these conditions have usually been multiple and widespread and have most often involved the greater curvature of the stomach. In these respects, the lesions differ from peptic ulcer, which has a predilection for the lesser curvature of the stomach, pylorus, and proximal duodenum.

The development of peptic ulcer in association with gastric hyperacidity has long been known to occur in persons exposed chronically to emotional stressful situations. Such has also been induced in experimental animals by subjecting them repeatedly to conflict situations. Lack of food to buffer gastric hypersecretion is an important factor in ulcer development. Conversely, the ingestion of antiacid preparations and properly timed food intake are means of preventing the ulceration.

HYPOTHALAMUS AND EMOTIONAL BEHAVIOR

Angry behavior, fearful behavior, and pleasure reactions are some of the aspects of emotional behavior to be dealt with in the present Section. The limbic system and the hypothalamus are heavily concerned in these forms of behavior. Although the limbic system constitutes a more or less autonomous system within the cerebrum - for example, an electrically-induced stimulus in the system usually is propagated only to other structures within the system - nonetheless this system has abundant interconnections with the cortex of the neocerebrum, particularly the cortex of the frontal and temporal lobes. Thus, the anatomical substratum of emotional behavior is widespread, and since it involves multiples of subcircuits, recurrent and otherwise, no specific behavior can be "located" or "centered" in any part of the brain. The hypothalamus fits, however, into the scheme in manifold ways. Integration and expression of emotional behavior are two attributes of the hypothalamus. The hypothalamus also contains neuron assemblies subserving the drive state directed to self-survival. For example, a cat which will not ordinarily attack a rat will exhibit well directed stalking and killing behavior during hypothalamic stimulation.[564]

Observations in Experimental Animals

That the hypothalamus is necessary for angry behavior was shown in cats in which all cerebral tissue rostral to the tuberal region was removed. Under these conditions angry behavior could easily be induced by relatively slight stimuli and was characterized by baring the teeth, arching the back, lashing the tail, spitting, snarling, biting, struggling, and clawing. Associated with the response was evidence of widespread sympathetic activity, such as piloerection, elevation of blood pressure, cardiac acceleration, sweating, and dilation of the pupils. The angry behavior could no longer

be induced after extirpation of the remaining hypothalamus and the subthalamus.[41,42] Ragelike reactions in cats have also been obtained by electrical stimulation of the more caudal part of the hypothalamus.[44,267,296]

The hypothalamus and midbrain have been explored for loci from which angry behavior could be elicited. Lesions placed bilaterally in the anteromedial part of the hypothalamus were found to transform formerly tame and friendly cats into savage animals,[278] and in other studies the same effect was obtained by damaging the region of the ventromedial nucleus bilaterally, including the so-called pallidohypothalamic tract.[44,569] Through electrical stimulation a locus from which angry defensive behavior could be elicited in cats was found in the perifornical region.[268] This observation was subsequently confirmed, and a second area, situated in the periaqueductal gray, in the region between the third and fourth cranial nerve nuclei, and acting autonomously, was also found effective in this respect.[274] Hence it was concluded that the neural apparatus necessary for the integration of the expression of anger lay not only in the caudolateral hypothalamus but also in the perifornical and periaqueductal regions. Moreover, through the implantation of crystalline acetylcholine together with physostigmine, loci for the elicitation of angry behavior were found in the lateral hypothalamic area, ventromedial nucleus (its dorsal part), and the posterior hypothalamic periventricular region.[166] The neural locus for growling (in the cat) as an aspect of angry behavior has been narrowed down to the tuberal region, and that for hissing, just above the tuberal region.[90]

Similar manifestations of anger in cats have been elicited by electrically stimulating limbic structures - namely, the amygdala (its medial part), olfactory tubercle, and the stria terminalis and its bed nucleus

near the septal region, on through the basomedial preoptic and anterior hypothalamic regions.[186,362] Focal destruction of the orbitofrontal cortex in the monkey has been followed by unbridled ferocity,[210,350] and damage of the hippocampal-fornical system in cats by a similar effect.[75] The fiber pathways concerned are funneled from limbic structures to the preoptic area, hypothalamus, and midbrain, in a manner described in a previous section. In general, it would appear that some of the components of the limbic lobe mentioned normally exert an inhibitory effect on the hypothalamus at a nodal point in the perifornical region situated near the rostral superior pole of the ventromedial nucleus, and that angry behavior is mediated by the periaqueductal gray through pathways still to be identified.

Less is known of the anatomical substratum underlying fearful behavior. Effective loci have been uncovered in cats by ablation experiments or by electrical stimulation, as revealed by the crouching, mewing, and dashing off in a slinking manner that occurs in response to hissing steam. Effective loci have also been found within and at the periphery of the perifornical region and on caudally through the lateral hypothalamic area into the region of the periaqueductal gray.[45,267,274]

Experimentation has revealed that pleasure reactions can be elicited from limbic structures and the hypothalamus. Expression of pleasure in cats (such as grooming and purring) is enhanced through stimulation of the dorsal hippocampus and septal region; septal stimulation in male cats leads to grooming and other pleasure reactions and sometimes to penile erection.[361,363] For pleasure reactions to be enhanced a wide area of the basal telencephalon and certain parts of the thalamus need to be intact.[365] A pleasurable feeling has been elicited on electrical stimulation in these and other

areas. The feeling has been such that a rat with indwelling electrodes in certain parts of its brain will repeatedly press a bar, setting off electrical stimulation in its brain, or walk over an electrified grid, in order to continue having this feeling (self-stimulation for reward).[416] The septal area is highly responsive, and positive loci for self-stimulation are also situated in the medial forebrain bundle in its hypothalamic course.[413-415] In the hypothalamus the highest rates of self-stimulation have been obtained from the far-lateral hypothalamus at the level of the infundibulum; electrical stimulation of the ventromedial nucleus inhibited this activity.[389] Some humans electrically stimulated in the septal area state that the stimulation produced a pleasurable or glowing feeling,[260] others a feeling of sex gratification. Postulated descending brain stem motor pathways in effecting pleasurable responses include the rubrospinal and tegmentospinal system.[469]

Lack of the capacity for anger and for fear are among the host of disturbances (Klüver-Bucy syndrome) resulting from bilateral ablations involving the frontotemporal part of the limbic system (amygdala, piriform cortex, and contiguous part of the hippocampal formation) in monkeys; among the other disturbances are hypersexuality of a bizarre nature, loss of discrimination of taste for thirst-quenching fluids, swallowing of any object placed in the mouth, and loss of awareness of what is harmful or painful such that a monkey will try to mouth a burning match. Thus, the ablations transformed the monkey from a normally aggressive into a placid creature incapable of anger or fear.[95,313,442,443] Other animal species, e.g., the cat, exhibit comparable behavior following ablation.[486]

The discovery that the syndrome just described was elicitable was preceded by the postulation[430] that the limbic lobe plays a fundamental

role in the elaboration and experiencing of emotion: "The hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their interconnections constitute a harmonious mechanism which may elaborate the functions of central emotion." The Klüver-Bucy syndrome has been considered traceable to interference with impulse conduction in any one or more of three systems: (1) hippocampus, to mamillary body, thence to the anterior thalamic nuclei, the cingular gyrus, and back by way of the retrosplenial cingular cortex to the hippocampal gyrus, then to the hippocampus,[430] (2) from the visual association cortex (areas 18 and 19) to the lateral and basal parts of the temporal lobe, thence to the hippocampal formation,[220] and (3) from the septal area and the reticular thalamic nuclei via the fornix to the hippocampus, then the entorhinal area, which would be the origin of a re-entrant pathway extending to the midbrain tegmentum by way of the stria medullaris thalami; entering the activating system in the rostral part of the dorsal midbrain tegmentum, the fibers would influence and modify the upstream patterns of neural activity in the reticular activating system.[6,7,558]

Observations in Man

Some of the disturbances observed in experimental animals have their counterparts in man.

RAGE REACTIONS. In one patient, attacks of rage resulted from scarring of the temporal lobe secondary to ear infection. The attacks began with a growling cry, soon followed by violent rage. Sometimes the patient would walk the streets screaming, with saliva running from his mouth. He would assault anyone in the vicinity. The attacks, which ceased after the scar had been resected, were presumed to have been due to a spread of discharges from the temporal lobe by way of limbic pathways to caudal hypothalamic

nuclei.[503] A man, later found to have a scarred temporal pole in association with hemangioma, was subject to epilepsy and spells of irritability and abusiveness, and while in a state of "epileptic furor" killed his wife.[560] Many other examples of ictal emotional outbursts occurring in the presence of temporal lobe lesions are on record.[566]

Lesions of the orbital neocortex and the rostral hypothalamus have led to similar changes in behavior. A laceration of the orbital surface of one frontal lobe with subsequent abscess formation transformed a previously cheerful and friendly child into a dull, morose, aggressive child who, on occasion, was deliberately savage. Recovery ensued as the abscess healed.[159] In another case, of chiasmal tumor that extended into the third ventricle, the patient acted like a wild animal.[125] Rage attacks may also occur occasionally in the presence of lesions as far back as the caudal hypothalamus, subthalamus, or even the midbrain and may be induced by manipulating the hypothalamus during operative procedures.[13]

OTHER BEHAVIORAL REACTIONS. Lesions involving rostral hypothalamic and adjoining structures tend to be associated with heightened activity of various kinds, while lesions involving the mamillary bodies and vicinity are associated with the reduced responsiveness, for instance, drowsiness, somnolence, apathy, or indifference. Both states may, however, be evident in the presence of caudal hypothalamic lesions, namely, somnolence during the day and agitation and delirium at night. Korsakoff's psychosis has been observed in association with an "ependymal cyst" of the third ventricle. This disorder may also be a feature of Wernicke's encephalopathy, a condition in which the mamillary body, rostral midbrain, and periependymal structures are damaged[13] (see Chapter 22). Hypersexuality, paroxysmal in form, has been observed in association with temporal lobe tumor or epilepsy,

and has consisted of sexual urges, genital sensations, and orgasm.[550] (The Klüver-Bucy syndrome is discussed in Chapter 7.)

AUTONOMIC DISCHARGE PATTERNS. Episodic diffuse autonomic discharges not initiated by external stimuli have been reported. Discharge patterns initiated by colloid cyst of the third ventricle include the following: (1) sweating, elevation of blood pressure, bradycardia, extrasystoles, and irregular respiration, (2) flushing of the face, pronounced bradycardia, and reduced respiratory rate, (3) hot flashes, lacrimation, and repeated yawning, (4) blanching of the face, copious cold sweats, shivering, and bradycardia, (5) painful epigastric crises, chills, attacks of violent anger, and hypothermia [94°F (34.5°C)], and (6) lying on the one side but not on the other, maximal pupillary dilatation, fluttering pulse, cessation of respiration, tonic rigidity of the body, and profound somnolence.[404,579] Disturbances of much the same nature in a patient in whom a colloid cyst was also found in the third ventricle, have been referred to collectively as "diencephalic autonomic epilepsy."[432]

MISCELLANEOUS CONDITIONS INVOLVING THE HYPOTHALAMUS

Catalepsy

In catalepsy (wavy flexibility) the limbs placed in any position by the examiner are actively maintained by the patient. When the examiner moves the forearm at the elbow the resistance offered by the muscles is inconstant. Facial immobility is also commonly noted. In experimental animals, catalepsy has been produced by lesions that damage certain diencephalic and related structures. Such animals exhibit increased muscle tonus of an extremely plastic nature such that they can be molded into a variety of postures and maintain the postures over a period of minutes or longer. In cats the condition results from lesions made in the retromamil-

lary region down to the level of the nucleus of the third nerve. A cat with a lesion in this region will remain immobilized in awkward postures for long periods of time.[280,451] In rats, catalepsy has been produced by lesions involving the lateral hypothalamus, thalamic radiations, the fields of Forel, and the substantia nigra, but was most pronounced following severe damage of the fields of Forel, mamillary peduncles, ventral tegmental area of Tsai, and the substantia nigra.[40] It is thought that the catalepsy thus produced may be related to a sleep state.[399]

Kleine-Levin Syndrome

This syndrome, which is rare, is characterized by recurring episodes of somnolence or hypersomnia. The patient may act normally after such an attack, or an attack may be followed by compulsive overeating, motor unrest, irritability, and mental confusion. There may also be episodes in which the patient is apathetic, fatuous, distracted, childishly querulous, and feels persecuted; he berates his relatives as though he were drunk, and has outbursts of laughter, strange singing, or shouting; afterward he may be gay and excited, often sexually.[119] In some instances, hallucinatory or schizophreniform episodes form a component of the attacks. Polydipsia, hyperhidrosis, and an increase in blood sugar may be additional features of an attack. Occasionally the syndrome alternates with narcoleptic attacks.[217,222]

Recurring every three to six months or so, the attacks usually last two or three days and are over with for a time, or they may continue for as long as six weeks[341] or even twelve weeks.[119] Adolescent males are most commonly affected, adolescent females rarely.[217,222] The syndrome has been observed in association with brain tumor, head injury, endocrine and metabolic disorders, and as a sequela of encephalitis and febrile

illnesses of uncertain cause. But as a rule a history of an antecedent illness cannot be uncovered. EEG recordings have yielded either a normal sleep pattern or minor nonspecific abnormalities. In one case, however, the EEG showed striking, nonspecific abnormalities during periods of hypersomnolence. These consisted of marked slowing of the background activity and generalized high voltage slow rhythms alternating with lower voltage faster rhythms. Sleep spindles were absent, making it doubtful that the attacks could be equated with sleep. The giving of methylphenidate (Ritalin) intravenously during attacks of hypersomnia - which probably increases the activity of the reticular activating system - causes behavioral arousal and an increase in frequency of the EEG rhythms. A periodic, reversible disturbance in brain function (of unknown cause) affecting subcortical mechanisms, including hypothalamic mechanisms, has been suggested as responsible for the disorder.[236] Decrease in heart rate during the "sleep" period has not been described, nor has skin resistance been measured. For these and other reasons, the existence of the Kleine-Levin syndrome as a nosological entity has been called into question, the alternative being that what is called the Kleine-Levin syndrome represents a wide variety of neurophysiological disorders.[422]

Hand-Schüller-Christian Disease

When involving the tuberoinfundibular region of the hypothalamus, this disease may be manifested by obesity with hypogonadism or dwarfism with sexual impotence, but diabetes insipidus is more frequent, occurring in about 60 percent of cases. Destruction at the base of the skull in the region of the sella turcica results from invasion by the xanthoma cells that characterize the lesion, and diagnostic punched-out lesions

are seen in the cranial vault. Exophthalmos may also occur.[74]

Infectious Diseases

In poliomyelitis infection, in which the hypothalamus commonly shares in the damage,[39] the chief clinical signs include hyperthermia or hypothermia and gastric stasis or hemorrhage. Months or even years after the acute stage has passed the patient may still show evidence of subclinical hypothalamic damage as revealed by special tests.[89] In a case of typhoid fever encephalitis with consequent obesity and atrophy of the genitals, examination of the hypothalamus revealed reduction in the cell population of the ventromedial, paraventricular, and supraoptic nuclei (author's observation). In a case of post-chickenpox encephalitis, in which hyperthermia, obesity, and hypothyroidism occurred, lesions were subsequently found in the tuberal region and in the supraoptic nuclei.[347]

Trauma

From the clinical standpoint, evidence of hypothalamic or pituitary damage following head injury is infrequent. Diabetes insipidus, transient or permanent, is an occasional sequela of closed head injury,[438,573] as is also anterior pituitary insufficiency.[497,573] In rare instances, both diabetes insipidus and anterior pituitary insufficiency are found in the same patient.[226] There is suggestive evidence that adiposogenital dystrophy might also result from closed head injury.[573]

Pathological studies have, by contrast, revealed a much higher incidence of pituitary damage (and to a less degree, also hypothalamic damage) following head trauma than revealed clinically - an incidence as high as 60 to 70 percent.[71,100,323] Pathological changes include necrosis of the hypophysial stalk or infundibular process, hemorrhage in the neurohypophysis generally, gliosis or fibrosis of the posterior

lobe, and infarction (ischemic necrosis) of the anterior lobe of the pituitary of varying degree, usually without hemorrhage.[133,134,226,323] Posterior lobe lesions, observed in 42 percent of cases of craniocerebral injury, usually occur in association with fracture involving the base of the sella turcica.[323] Infarction of the anterior lobe following head trauma carries an incidence of about 22 percent.[100,323] No correlation has been found between the occurrence of the necrosis and the severity of the head injury or the type or location of the injury. Shock observed clinically and the finding of severe swelling of the brain and pituitary postmortem have consistently been noted in cases of anterior pituitary infarction. The infarction is considered to be due (1) to rupture of the hypophysial stalk (and its hypophysial portal vessels),[134] (2) to compression of hypophysial portal veins in their course beneath the diaphragma sella as a consequence of swelling of the pituitary,[323] and (3) to hypoxia resulting from traumatic shock.[420]

REFERENCES

1. ABRAMS, R. L., PARKER, M. L., BLANCO, S., REICHLIN, S., and DAUGHADAY, W. H. Hypothalamic regulation of growth hormone secretion. Endocrinology 78:605, 1966.

2. ADAMS, J. H., DANIEL, P. M., and PRICHARD, M. M. L. Distribution of the hypophysial portal blood in the anterior lobe of the pituitary gland. Endocrinology 75:120, 1964.

3. ADAMS, J. H., DANIEL, P. M., and PRICHARD, M. M. L. Observations on the portal circulation of the pituitary gland. Neuroendocrinology 1:193, 1966.

4. ADAMS, J. H., DANIEL, P. M., and PRICHARD, M. M. L. Transection of the pituitary stalk in man. Anatomical changes in the pituitary glands of 21 patients. J. Neurol. Neurosurg. Psychiat. 29:545, 1966.

5. ADEY, W. R., BUCHWALD, N. A., and LINDSLEY, D. F. Amygdaloid, pallidal, and peripheral influences on mesencephalic unit firing patterns with reference to mechanisms of tremor. EEG Clin. Neurophysiol. 12:21, 1960.

6. ADEY, W. R., DUNLOP, C. W., and SUNDERLAND, S. A survey of rhinencephalic interrelations with the brainstem. J. Comp. Neurol. 110:173, 1958.

7. ADEY, W. R., MERRILLES, N. R. C., and SUNDERLAND, S. The entorhinal area; behavioral, evoked potential, and histological studies of its interrelationships with brain-stem regions. Brain 79:414, 1956.

8. ADEY, W. R., SUNDERLAND, S., and DUNLOP, C. W. The entorhinal area. Electrophysiological studies of its interrelations with rhinencephalic structures and the brain stem. EEG Clin. Neurophysiol. 9:309, 1957.

9. AKERT, K. The anatomical substrate of sleep. Progr. Brain Res. 18:9, 1965.

10. AKIMOTO, H., YAMAGUCHI, N., OKABE, K., et al. On the sleep induced through electrical stimulation of dog thalamus. Folia Psychiat. Neurol. Jap. 10:117, 1956.

11. AKMAYEV, I. G. Morphological aspects of the hypothalamic-hypophysial system. 1. Fibers terminating in the neurohypophysis of mammals. Ztschr. Zellforsch. 96:609, 1969.

12. ALLEN, B. M. The relation of the pituitary and thyroid glands of Bufo and Rana to iodine and metamorphosis. Biol. Bull. 36:405, 1919.

13. ALPERS, B. J. Personality and emotional disorders associated with hypothalamic lesions. A. Res. Nerv. Ment. Dis., Proc. 20:725, 1940.

14. ANAND, B. K., and BROBECK, J. R. Localization of a "feeding center" in the hypothalamus of the rat. Proc. Soc. Exp. Biol. Med. 77:323, 1951.

15. ANAND, B. K., and BROBECK, J. R. Hypothalamic control of food intake in rats and cats. Yale J. Biol. Med. 24:123, 1951.

16. ANAND, B. K., CHHINA, G. S., and SINGH, B. Effect of glucose on the activity of hypothalamic "feeding centers." Science 138:597, 1962.

17. ANAND, B. K., and DUA, S. Blood sugar changes induced by electrical stimulation of the hypothalamus in the cat. Indian J. Med. Sci. 43:123, 1955.

18. ANAND, B. K., DUA, S., and CHHINA, G. S. Effect of neocortical lesions over food intake. Indian J. Med. Res. 49:491, 1961.

19. ANAND, B. K., SUBBERWAL, W., MANCHANDA, S. K., and SINGH, B. Glucoreceptor mechanism in the hypothalamic feeding centres. Indian J. Med. Res. 49:717, 1961.

20. ANDERSON, E., BATES, R. W., HAWTHORNE, E., HAYMAKER, W., KNOWLTON, K., RIOCH, D. McK., SPENCE, W. T., and WILSON, H. The effects of midbrain and spinal cord transection on endocrine and metabolic functions with postulation of a midbrain hypothalamico-pituitary activating system. Recent Progr. Hormone Res. 13:21, 1957.

21. ANDERSON, E. M., and COLLIP, J. B. Thyreotropic hormone of anterior pituitary. Proc. Soc. Exp. Biol. Med. 30:680, 1933.

22. ANDERSON, E., and HAYMAKER, W. Elaboration of hormones by pituitary cells growing in vitro. Proc. Soc. Exp. Biol. Med. 33:313, 1935.

23. ANDERSON, E., RIOCH, D. McK., and HAYMAKER, W. Disturbances in blood sugar regulation in animals subjected to transection of the brain stem. Acta Neuroveg. 5:132, 1952.

24. ANDERSSON, B. "Polydipsia, Antidiuresis and Milk Ejection Caused by Hypothalamic Stimulation." In: The Neurohypophysis, H. HELLER (ed.). New York, Academic Press, 1957, p. 131.

25. ANDERSSON, B. Cold defense reactions elicited by electrical stimulation within the septal area of the brain in goats. Acta Physiol. Scandinav. 41:90, 1957.

26. ANDERSSON, B., DALLMAN, M. F., and OLSSON, K. Evidence for a hypothalamic control of renal sodium excretion. Acta Physiol. Scandinav. 75:496, 1969.

27. ANDERSSON, B., GRANT, R., and LARSSON, S. Central control of heat loss mechanisms in the goat. Acta Physiol. Scandinav. 37:261, 1956.

28. ANDERSSON, B., and McCANN, S. M. Further study of polydipsia evoked by hypothalamic stimulation in the goat. Acta Physiol. Scandinav. 33:333, 1955.

29. ANDERSSON, B., and PERSSON, N. Pronounced hypothermia elicited by prolonged stimulation of the "heat loss centre" in unanesthetized goats. Acta Physiol. Scandinav. 41:277, 1957.

30. ANGELSTEIN, I. Beitrag zur Pathogenese der Akromegalie. Dtsch. Ztschr. Nervenheilk. 170:337, 1953.

31. APLEY, J. Sexual precocity in a boy after measles encephalomyelitis. Arch. Dis. Childh. 27:584, 1952.

32. APPENZELLER, O., and SNYDER, R. D. Autonomic failure with persistent fever in cerebral gigantism. J. Neurol. Neurosurg. Psychiat. 32:123, 1969.

33. AREES, E. A., and MAYER, J. Anatomical connections between medial and lateral regions of the hypothalamus concerned with food intake. Science 157:1574, 1967.

34. AREY, L. B. Developmental Anatomy. A Textbook and Laboratory Manual of Embryology, 4th rev. ed. Philadelphia, Saunders, 1944, pp. 200, 217.

35. AUSTIN, M. G., and BERRY, J. W. Observations on one hundred cases of heatstroke. J.A.M.A. 161:1525, 1956.

36. BAILEY, P. Intracranial Tumors, 2d ed. Springfield, Thomas, 1948, p. 88.

37. BAILEY, P., and SWEET, W. H. Effects on respiration, blood pressure and gastric motility of stimulation of orbital surface of frontal lobe. J. Neurophysiol. 3:276, 1940.

38. BAIN, H. W., DARTE, J. M. M., KEITH, W. S., and KRUYFF, E. The diencephalic syndrome of early infancy due to silent brain tumor, with special reference to treatment. Pediatrics 38:473, 1966.

39. BAKER, A. B., CORNWELL, S., and BROWN, I. A. Poliomyelitis. VI. Hypothalamus, Arch. Neurol. Psychiat. 68:16, 1952.

40. BALAGURA, S., WILCOX, R. H., and COSCINA, D. V. The effect of diencephalic lesions on food intake and motor activity. Physiol. Behav. 4:629, 1969.

41. BARD, P. A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. Amer. J. Physiol. 84:490, 1928.

42. BARD, P. On emotional expression after decortication with some remarks on certain theoretical views. Psychol. Rev. 41:309, 424, 1934.

43. BARD, P. Medical Physiology, 10th ed. St. Louis, Mosby, 1956, p. 1220.

44. BARD, P., and MOUNTCASTLE, V. B. Some forebrain mechanisms in expression of anger. A. Res. Nerv. Ment. Dis., Proc. 27:362, 1948.

45. BARD, P., and RIOCH, D. McK. A study of four cats deprived of neocortex and additional portions of the forebrain. Johns Hopk. Hosp. Bull. 60:73, 1937.

46. BARGMANN, W. Electronmikroskopische Untersuchungen an der Neurohypophyse. 2nd Internat. Sympos. Neurosecretion, Lund, 1957. Berlin, Springer, 1958, p. 4.

47. BARLOW, E. D., and De WARDENER, H. E. Compulsive water drinking. Quart. J. Med., n.s. 28:235, 1959.

48. BARRACLOUGH, M. A., JONES, J. J., and LEE, J. Production of vasopressin by an aplastic oat cell carcinoma of the bronchus. Clin. Sci. 31:135, 1966.

49. BARRIS, R. W., and INGRAM, W. R. The effect of experimental hypothalamic lesions on blood sugar. Amer. J. Physiol. 114:555, 1936.

50. BARTTER, F. C., and SCHWARTZ, W. B. The syndrome of inappropriate secretion of antidiuretic hormone. Amer. J. Med. 42:790, 1967.

51. BAUER, H. G. Endocrine and other manifestations of hypothalamic disease. J. Clin. Endocrinol. Metab. 14:13, 1954.

52. BAXTER, C. R., and TESCHAN, P. E. Atypical heat stroke, with hypernatremia, acute renal failure, and fulminating potassium intoxication. A.M.A. Arch. Int. Med. 101:1040, 1958.

53. BEATON, L. E., and HERRMANN, J. D. Hyperthermia following injury to the preoptic region. Arch. Neurol. Psychiat. 53:150, 1945.

54. BEATON, L. E., and LEININGER, C. R. Spinal distribution of thermoregulatory pathways in monkey. J. Neurophysiol. 6:37, 1943.

55. BEATON, L. E., LEININGER, C., McKINLEY, W. A., MAGOUN, H. W., and RANSON, S. W. Neurogenic hyperthermia and its treatment with soluble pentobarbital in the monkey. Arch. Neurol. Psychiat. 49:518, 1943.

56. BEATTIE, J., and SHEEHAN, D. The effects of hypothalamic stimulation on gastric motility. J. Physiol. 81:218, 1934.

57. BECK, E., and DANIEL, P. M. Changes in the human hypothalamus after pituitary stalk section or hypophysectomy. J. Clin. Path. 12:577, 1959.

58. BECK, E., and DANIEL, P. M. Degeneration and Regeneration in the Hypothalamus. Proc. Anat. Soc. Great Britain and Ireland, London, Taylor & Francis, 1961, p. 60.

59. BEERNINK, F. J., and McKAY, D. G. Pituitary insufficiency associated with pregnancy, panpituitarism, and diabetes insipidus. Amer. J. Obst. Gynec. 84:318, 1962.

60. BELLOWS, R. T., and VAN WAGENEN, W. P. The effect of resection on the olfactory, gustatory and trigeminal nerves on water drinking in dogs without and with diabetes insipidus. Amer. J. Physiol. 126:13, 1939.

61. BENSON, G. K., and FOLLEY, S. J. Oxytocin as stimulator for the release of prolactin from the anterior pituitary. Nature 177:700, 1956.

62. BENZINGER, T. H. On physical heat regulation and the sense of temperature in man. Proc. Nat. Acad. Sci. 45:645, 1959.

63. BENZINGER, T. H. "The Thermal Homeostasis of Man." In: Homeostasis and Feedback Mechanisms, G. M. HUGHES (ed.). Sympos. Soc. Exp. Biol., no. 18, New York, Academic Press, 1964, p. 49.

64. BENZINGER, T. H., PRATT, A. W., and KITZINGER, C. The thermostatic control of human metabolic heat production. Proc. Nat. Sci. 47:730, 1961.

65. BERG, O., and HANLEY, J. Narcolepsy in two cases of multiple sclerosis. Acta Neurol. Scandinav. 39:252, 1963.

66. BERGLAND, R. M., and TORACK, R. M. An electron microscopic study of the human infundibulum. Ztschr. Zellforsch. 99:1, 1969.

67. BERRY, R. G., and SCHLEZINGER, N. S. Rathke-cleft cysts. A.M.A. Arch. Neurol. 1:62/48, 1959.

68. BIGGART, J. H. The anatomical basis for resistance to pituitrin in diabetes insipidus. J. Path. Bact. 44:305, 1937.

69. BING, J. F., GLOBUS, J. H., and SIMON, H. Pubertas praecox: A survey of the reported cases and verified anatomical findings, with particular reference to tumors of the pineal body. J. Mt. Sinai Hosp. 4:935, 1938.

70. BIRNBAUM, D., WAJSBORT, J., and FELDMAN, S. Changes in bile secretion produced by hippocampal and hypothalamic stimulation. Exp. Neurol. 24:265, 1969.

70a. BODECHTEL, G. Zur Klinik des Nervensystems. Verh. dtsch. Ges. inn. Med. 54:57, 1948.

71. BOLTZ, K., and SKALA, O. Zur Entstehung traumatischer Hypophysenschäden. Acta Med. Leg. Soc. 15:45, 1962.

72. BORELL, U. On the transport route of the thyrotropic hormone, the occurrence of the latter in different parts of the brain and its effect on thyroidea. Acta Med. Scandinav., suppl. 161, 1945.

73. BORNSTEIN, B. Tumor des Tectum mesencephali unter dem Bilde der Encephalitis lethargica. Jahrb. Psychiat. Neurol. 49:46, 1933.

74. BOSHES, B. "Syndromes of the Diencephalon. The Hypothalamus and Hypophysis." In: Handbook of Clinical Neurology, vol. 2. P. J. VINKEN and G. W. BRUYN (eds.). Amsterdam, North-Holland Publ. Co., 1969, p. 432.

75. BRADY, S. V. "Emotional Behavior." In: Handbook of Physiology, J. Field, H. W. Magoun and V. E. Hall (eds.), sect. 1, vol. III. Washington, D.C., Amer. Physiol. Soc., 1960, p. 1529.

76. BRAIN, R. The physiological basis of consciousness. A critical review. Brain 81:426, 1958.

77. BRASEL, J. A., WRIGHT, J. C., WILKINS, L., and BLIZZARD, R. M. An evaluation of seventy-five patients with hypopituitarism beginning in childhood. Amer. J. Med. 38:484, 1965.

78. BREMER, F., and TERZUOLO, C. Contribution à l'étude des méchanismes physiologiques du maintien de l'activité vigil du cerveau. Arch. Internat. Physiol. 62:157, 1954.

79. BRICOLO, A. Insomnia of the bilateral stereotactic thalamotomy in man. J. Neurol. Neurosurg. Psychiat. 30:154, 1967.

80. BRISMAN, R., and CHUTORIAN, A. M. Inappropriate ADH secretion with unique features in a child with a hypothalamic glioma. Trans. Amer. Neurol. Assn. 94:110, 1969.

81. BRITT, B. A., and KALOW, W. Hyperrigidity and hyperthermia associated with anesthesia. Ann. N. Y. Acad. Sci. 151:947, 1968.

82. BROCKHAUS, H. Beitrag zur normalen Anatomie des Hypothalamus und der Zona incerta beim Menschen. Versuch einer architektonischen Gliederung. J. Psychol. Neurol. 51:96, 1942.

83. BROOKS, C. McC., ISHIKAWA, T., KOIZUMI, K., and LU, H. H. Activity of neurons in the paraventricular nucleus of the hypothalamus and its control. J. Physiol. 182:217, 1966.

84. BROOKS, C. McC., and LAMBERT, E. F. A study of the effect of limitation of food intake and the method of feeding on the rate of weight gain during hypothalamic obesity in the albino rat. Amer. J. Physiol. 147:659, 1946.

85. BROOKS, C. McC., MARINE, D. N., and LAMBERT, E. F. A study of the food-feces ratios and of the oxygen consumption of albino rats during various phases of experimentally produced obesity. Amer. J. Physiol. 147:717, 1946.

86. BROUGHAM, M., HEUSNER, A. P., and ADAMS, R. D. Acute degenerative changes in adenomas of the pituitary body - with special reference to pituitary apoplexy. J. Neurosurg. 7:421, 1950.

87. BROUWER, B. Positive and negative aspects of hypothalamic disorders. J. Neurol. Neurosurg. Psychiat. 13:16, 1950.

88. BROWN, G. A., STIMMLER, L., and LINES, J. G. Growth hormone-induced nitrogen retention in children of short stature. Arch. Dis. Childh. 42:239, 1967.

89. BROWN, I. A., and BARRIS, H. Poliomyelitis: A clinical evaluation of hypothalamic involvement. Arch. Neurol. Psychiat. 72:60, 1954.

90. BROWN, J. L., HUNSPERGER, R. W., and ROSVOLD, H. E. Defence, attack, and flight elicited by electrical stimulation of the hypothalamus of the cat. Exp. Brain Res. 8:113, 1969.

91. BROWN-GRANT, K. "The Control of TSH Secretion." In: The Pituitary Gland, G. W. HARRIS and B. T. DONOVAN (eds.), vol. 2. Berkeley, Univ. California Press, 1966, p. 235.

92. BRUCH, H. Psychotherapy in primary anorexia nervosa. J. Nerv. Ment. Dis. 150:51, 1970.

93. BRUTKOWSKI, S., FONBERG, E., KREINER, J., MEMPEL, E., and SYCHOWA, B. Aphagia and adipsia in a dog with a bilateral complete lesion of the amydaloid complex. Acta Biol. Exp. 22:43, 1962.

94. BUCHWALD, N. A., and ERVIN, F. R. Evoked potentials and behavior. A study of the responses to cortical stimulation in the awake, unrestrained animal. EEG Clin. Neurophysiol. 9:477, 1957.

95. BUCY, P. C., and KLÜVER, H. Anatomic changes secondary to temporal lobectomy. Arch. Neurol. Psychiat. 44:1142, 1940.

96. BURDENKO, N., and MOGILNITZKI, B. Zur Pathogenese einiger Formen des runden Magendarmgeschurs. Ztschr. ges. Neurol. Psychiat. 103:42, 1926.

97. BYROM, F. B., and RUSSELL, D. S. Ependymal cyst of the third ventricle. Lancet 223:278, 1932.

98. CARROLL, B. J., PEARSON, M. J., and MARTIN, F. I. R. Evaluation of three acute tests of hypothalamic-pituitary-adrenal function. Metabolism 18:476, 1969.

99. CASTAIGNE, P., and ESCOUROLLE, R. Etude topographique des lésions anatomique dans les hypersomnies. Rev. Neurol. 1:547, 1967.

100. CEBELLOS, R. Pituitary changes in head trauma. Alabama J. Med. Sci. 3:185, 1966.

101. CHAMBLIN, M., DAVIDOFF, L. M., and FEIRING, E. H. Ophthalmologic changes produced by pituitary tumors. Amer. J. Ophthal. 40:353, 1955.

102. CHOUX, M., BAURAND, C., PIERRON, H., and VIGOUROUX, R. P. Lipo-atrophie cachectisante par tumeur de la partie antérieure du plancher du III^{e} ventricule ("syndrome de Russell"). Revue générale à propos de 2 observations. Neuro-Chirurgie 15:59, 1969.

103. CHRIST, J. Zur Anatomie des Tuber cinereum beim erwachsenen Menschen. (Mit besonderer Berücksichtigung der Beziehungen zur Hypophyse.) Dtsch. Ztschr. Nervenheilk. 165:340, 1951.

104. CHRIST, J. Über den Nucleus infundibularis beim erwachsenen Menschen. Acta Neuroveg. 3:267, 1951.

105. CHRIST, J. F. "Nerve Supply, Blood Supply and Cytology of the Neurohypophysis." In: The Pituitary Gland, G. W. HARRIS and B. T. DONOVAN (eds.), vol. 3. Berkeley, Univ. California Press, 1966, p. 62.

106. CHRIST, J. F. "Derivation and Boundaries of the Hypothalamus, with Atlas of Hypothalamic Grisea." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 13.

107. CICCARELLI, E. C., and HUTTENLOCHER, P. R. Diencephalic tumor. A cause of infantile nystagmus and cachexia. Arch. Ophthal. 78:350, 1967.

108. COBO, E., GAITAN, E., MIZRACHI, M., and STRADA, G. Neurohypophyseal hormone release in the human. I. Experimental study during pregnancy. Amer. J. Obst. Gynecol. 91:905, 1965.

109. COBO, E., De BERNAL, M. M., GAITAN, E., and QUINTERO, C. A. Neurohypophyseal hormone release in the human. II. Experimental study during lactation. Amer. J. Obst. Gynecol. 97:519, 1967.

110. COBO, E., De BERNAL, M. M., QUINTERO, C. A., and CUADRADO, E. Neurohypophyseal hormone release in the human. III. Experimental study during labor. Amer. J. Obst. Gynecol. 101:479, 1968.

111. COBURN, J. W., and REBA, R. C. Potassium depletion in heat stroke: A possible etiologic factor. Mil. Med. 131:678, 1966.

112. COLLIP, J. B., ANDERSON, E. M., and THOMSON, D. L. The adrenotrophic hormone of the anterior pituitary lobe. Lancet 2:347, 1933.

113. COOPER, K. E. Temperature regulation and the hypothalamus. Brit. Med. Bull. 22:238, 1966.

114. CORT, J. H., and LICHARDUS, B. The role of the hypothalamus in the renal response to the carotid sinus pressor reflex. Physiol. Bohemoslov. 12:389, 1963.

115. COYLE, J. T. Chiasmatic arachnoiditis. A case report and review. Amer. J. Ophthal. 68:345, 1969.

116. COX, L. B. Tumours of the base of the brain: Their relation to pathological sleep and other changes in the conscious state. Med. J. Austr. 2:742, 1937.

117. CRAIG, W. M., and LILLIE, W. I. Chiasmal syndrome produced by chronic local arachnoiditis. Report of 8 cases. Arch. Ophthal. 5:558, 1931.

118. CRANSTON, W. I. Temperature regulation. Brit. Med. J. 2:69, 1966.

119. CRITCHLEY, M. Periodic hypersomnia and megaphagia in adolescent males. Brain 85:627, 1962.

120. CROSBY, E. C., and SHOWERS, M. J. C. "Comparative Anatomy of the Preoptic and Hypothalamic Areas." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 61.

121. CROSBY, E. C., and WOODBURNE, R. T. The comparative anatomy of the preoptic area and the hypothalamus. A. Res. Nerv. Ment. Dis., Proc. 20:52, 1940.

122. CROSS, B. A., and GREEN, J. D. Activity of single neurones in the hypothalamus: Effect of osmotic and other stimuli. J. Physiol. 148:554, 1959.

123. CRYER, P. E., and DAUGHADAY, W. H. Regulation of growth hormone secretion in acromegaly. J. Clin. Endocrinol. Metab. 29:386, 1969.

124. CUNEO, H. M. Ectopic pinealomas. J. Neurosurg. 17:161, 1960.

125. CUSHING, H. W. Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System. Springfield, Thomas, 1932, p. 175.

126. CUSHING, H. Peptic ulcers and the interbrain. Surg. Gynec. Obst. 55:1, 1932.

127. CUSHING, H. Basophil adenomas of pituitary body and their clinical manifestation (pituitary basophilism). Bull. Johns Hopk. Hosp. 50:137, 1932.

128. DANDY, W. E. Section of the human hypophyseal stalk: Its relation to diabetes insipidus and hypophyseal functions. J.A.M.A. 114:312, 1940.

129. D'ANGELO, S. A., and TRAUM, R. E. An experimental analysis of the hypothalamic-hypophysial-thyroid relationship in the rat. Ann. N. Y. Acad. Med. 72:239, 1958.

130. DANIEL, P. M. The blood supply of the hypothalamus and pituitary gland. Brit. Med. Bull. 22:202, 1966.

131. DANIEL, P. M., and PRICHARD, M. M. L. Anterior pituitary necrosis. Infarction of the pars distalis produced experimentally in the rat. Quart. J. Exp. Physiol. 41:215, 1956.

132. DANIEL, P. M., PRICHARD, M. M. L., and SCHURR, R. H. Extent of the infarct in the anterior lobe of the human pituitary gland after stalk section. Lancet 1:1101, 1958.

133. DANIEL, P. M., PRICHARD, M. M. L., and TREIP, C. S. Traumatic infarction of the anterior lobe of the pituitary gland. Lancet 2:927, 1959.

134. DANIEL, P. M., and TREIP, C. S. "Lesions of the Pituitary Gland Associated with Head Injuries." In: The Pituitary Gland, G. W. HARRIS and B. T. DONOVAN (eds.), vol. 2. Berkeley, Univ. California Press, 1966, p. 519.

135. DARMADY, E. M., OFFER, J., PRINCE, J., and STRANACK, F. The proximal convoluted tubule in the renal handling of water. Lancet 2:1254, 1964.

136. DAVEY, L. M., KAADA, B. R., and FULTON, J. F. Effects of gastric secretion of frontal lobe stimulation. A. Res. Nerv. Ment. Dis., Proc. 29:617, 1950.

137. DAVIS, L., CLEVELAND, D., and INGRAM, W. R. Carbohydrate metabolism. The effect of hypothalamic lesions and stimulation of the autonomic nervous system. Arch. Neurol. Psychiat. 33:592, 1935.

138. DAVIS, R. A., BROOKS, F. B., and STECKEL, D. C. Gastric secretory changes after anterior hypothalamic lesions. Amer. J. Physiol. 215:600, 1968.

139. DAVISON, C. Disturbances of temperature regulation in man. A clinicopathologic study. A. Res. Nerv. Ment. Dis., Proc. 20:774, 1940.

140. DAVISON, C., and DEMUTH, E. L. Disturbances in sleep mechanism. A clinicopathologic study. I. Lesions at the cortical level. Arch. Neurol. Psychiat. 53:395, 1945.

141. DAVISON, C., and DEMUTH, E. L. Disturbances in sleep mechanism. A clinicopathologic study. II. Lesions at the corticodiencephalic level. Arch. Neurol. Psychiat. 54:241, 1945.

142. DAVISON, C., and DEMUTH, E. L. Disturbances in sleep mechanism. A clinicopathologic study. III. Lesions at the diencephalic level (hypothalamus). Arch. Neurol. Psychiat. 55:111, 1946.

143. DAVISON, C., and DEMUTH, E. L. Disturbances in sleep mechanism. A clinicopathologic study. IV. Lesions at the mesencephalometencephalic level. Arch. Neurol. Psychiat. 55:126, 1946.

144. DAVISON, C., and FRIEDMAN, E. D. Poikilothermia with hypothalamic lesions; a clinicopathologic study. Arch. Neurol. Psychiat. 38:1271, 1937.

145. DAVISON, C., and SELBY, N. E. Hypothermia in cases of hypothalamic lesions. Arch. Neurol. Psychiat. 33:570, 1935.

146. DAWSON, A. B. Early secretory activity in the hypothalamic nuclei and neurohypophysis in the rat; determined by selective staining. J. Morph. 118:549, 1966.

147. DAWSON, B. H. The blood vessels of the human optic chiasma and their relation to those of the hypophysis and hypothalamus. Brain 81:207, 1958.

148. DEBACKERE, M., PEETERS, G., and TUYTTENS, N. Reflex release of an oxytocic hormone by stimulation of genital organs in male and female sheep studied by a cross circulation technique. J. Endocrinol. 22:321, 1961.

149. de GROOT, J., and HARRIS, G. W. Hypothalamic control of the anterior pituitary gland and blood lymphocytes. J. Physiol. 111:335, 1950.

150. de GROOT, J., and HARTFIELD, J. E. Quantitative changes in rat pituitary neurosecretory material in altered adrenocortical function. Acta Neuroveg. 22:177, 1961.

151. DELGADO, J. M. R., and ANAND, K. Increased food intake induced by electrical stimulation of the lateral hypothalamus. Amer. J. Physiol. 172:162, 1953.

152. DELL, P., and OLSON, R. Projections "secondaires" mésencéphaliques, diencéphaliques et amygdaliennes des afférences viscérales vagales. C. R. Soc. Biol. 145:1088, 1951.

153. de WIED, D., WITTER, A., VERSTEEG, D. H. G., and MULDER, A. H. Release of ACTH by substances of central nervous system origin. Endocrinology 85:561, 1969.

154. DEY, F. L. Genital changes in female guinea pigs resulting from destruction of the median eminence. Anat. Rec. 87:85, 1943.

155. DEY, F. L., FISHER, C., BERRY, C. M., and RANSON, S. W. Disturbances in reproductive functions caused by hypothalamic lesions in female guinea pigs. Amer. J. Physiol. 129:39, 1940.

156. DIEPEN, R. "Der Hypothalamus." In: von Möllendorff's Hdb. d. mikro. Anat. d. Menschen, Nervensystem, vol. IV, pt. 7. Berlin, Springer, 1962.

157. DONOVAN, B. T., and van der WERFFTENBOSCH, J. J. Oestrus in winter following hypothalamic lesions in the ferret. Nature 178:745, 1956.

158. DOTT, N. M. Bitemporal hemianopia in relation to hydrocephalic distention of the third ventricle. Brit. Med. J. 2:296, 1936.

159. DOTT, N. M. "Surgical Aspects of the Hypothalamus." In: The Hypothalamus, W. E. LeG. CLARK et al. (eds.). Edinburgh, Oliver & Boyd, 1938, p. 131.

160. DOUGLAS, W. W., and PATON, W. O. M. The hypothermic and antipyretic effect of preparations of ACTH. Lancet 262:342, 1952.

161. DOWNMAN, C. B. B. Skeletal muscle reflexes of splanchnic and intercostal nerve origin in acute spinal and decerebrate cats. J. Neurophysiol. 18:217, 1955.

162. DRACHMAN, D. B., and GUMNIT, R. J. Periodic alteration of consciousness in the "Pickwickian" syndrome. Arch. Neurol. 6:471, 1962.

163. DRIGGS, M., and SPATZ, H. Pubertas praecox bei einer hyperplastischen Missbildung des Tuber cinereum. Virchows Arch. path. Anat. 305:567, 1939.

164. DuBOIS, E. F. Why are fever temperatures over 106°F. rare? Amer. J. Med. Sci. 217:361, 1949.

165. EDMONDSON, H. T., GINDIN, R. A., and PEEBLES, G. C. Cerebral lesions as a cause of esophageal ulceration. Surgery 64:720, 1968.

166. EGLIN, J. M. A Study of Behavioral Effects of Following Intra-hypothalamic Injection of Acetylcholine with Eserine in the Waking Animal. Thesis, Yale Univ. Sch. Med., 1953.

167. EHNI, G., and ECKLES, N. E. Interruption of the pituitary stalk in the patient with mammary cancer. J. Neurosurg. 16:628, 1959.

168. EICHLER, A. C., McFEE, A. S., and ROOT, H. D. Heat stroke. Amer. J. Surg. 118:855, 1969.

169. EICHNER, D. Über funktionelle Kernschwellung in den Nuclei supraoptici und paraventricularis des Hundes bei experimentellen Durstzuständen. Ztschr. Zellforsch. 37:406, 1952.

170. EISENFELD, A. J., and AXELROD, J. Effect of steroid hormones, ovariectomy, estrogen pretreatment, sex and immaturity on the distribution of ^{3}H-estradiol. Endocrinology 79:38, 1966.

171. ELEFTHERIOU, B. E., DESJARDINS, C., PATTISON, M. L., NORMAN, R. L., and ZOLOVICK, A. J. Effects of amygdaloid lesions on hypothalamic-hypophyseal growth-hormone activity. Neuroendocrinology 5:132, 1969.

172. ELEFTHERIOU, B. E., and ZOLOVICK, A. J. Effect of amygdaloid lesions on plasma and pituitary thyrotropin levels in the deermouse. Proc. Soc. Exp. Biol. Med. 127:671, 1968.

173. ELEFTHERIOU, B. E., ZOLOVICK, A. J., and PEARSE, R. Effect of amygdaloid lesions on the pituitary-adrenal axis in the deermouse. Proc. Soc. Exp. Biol. Med. 122:226, 1966.

174. ELIASSON, S. G. "Central Control of Digestive Function." In: Handbook of Physiology, sect. 1, vol. II, J. FIELD, H. W. MAGOUN and V. E. HALL (eds.). Baltimore, Williams & Wilkins, 1960, p. 1163.

175. ELKINGTON, S. G. Pituitary adenoma. Preoperative symptomatology in a series of 260 patients. Brit. J. Ophthal. 52:322, 1968.

176. ELWERS, M., and CRITCHLOW, V. Precocious ovarian stimulation following hypothalamic and amygdaloid lesions in rats. Amer. J. Physiol. 198(2): 381, 1960.

177. ERICKSON, T. C. Neurogenic hyperthermia. (A clinical syndrome and its treatment.) Brain 62:172, 1939.

178. ESPINOSA, R. E., and RANDALL, R. V. Early symptoms and signs of chromophobe adenoma. Med. Clin. N. Amer. 52:827, 1968.

179. EVANS, H. M., and LONG, J. A. The effect of anterior lobe administered intraperitoneally upon growth and maturity and the oestrous cycles of the rat. Anat. Rec. 21:62, 1921.

180. EVANS, J. I., and OSWALD, I. Some experiments in the chemistry of narcoleptic sleep. Brit. J. Psychiat. 112:401, 1966.

181. EVERETT, J. W. Luteotrophic function of autografts of the rat hypophysis. Endocrinology 54:685, 1954.

182. EVERETT, J. W. Functional corpora lutea maintained for months by autografts of rat hypophyses. Endocrinology 56:786, 1956.

183. FAÇON, E., STERIDE, M., and WERTHEIM, N. Hypersomnie prolongée engendrée par les lésions bilatérales du système activateur médial. Le syndrome thrombotique de la bifurcation du tronc basilare. Rev. Neurol. 2:117, 1958.

184. FARQUHARSON, R. F. Simmonds' Disease. Extreme Insufficiency of the Adenohypophysis. Springfield, Thomas, 1950.

185. FELDBERG, W., and MYERS, R. D. Effects on temperature of amines injected into the cerebral ventricles. A new concept of temperature regulation. J. Physiol. 173:226, 1964.

186. FERNANDEZ de MOLINA, A., and HUNSPERGER, R. W. Central representation of affective reactions in forebrain and brain stem. Electrical stimulation of amygdala, stria terminalis, and adjacent structures. J. Physiol. 145:251, 1959.

187. FERRIER, P. E., and STONE, E. F., Jr. Familial pituitary dwarfism associated with an abnormal sella turcica. Pediatrics 43:858, 1969.

188. FERRIS, E. B., Jr., BLANKENHORN, M. A., ROBINSON, H. W., and CULLEN, G. E. Heat stroke: Clinical and chemical observations on 44 cases. J. Clin. Invest. 17:249, 1938.

189. FINLEY, K. Angio-architecture of the hypothalamus and its peculiarities. A. Res. Nerv. Ment. Dis., Proc. 20:286, 1940.

190. FISHER, R. L., and Di CHARO, G. The small sella. Amer. J. Roentgenol. 91:996, 1964.

191. FITZPATRICK, R. J. "The Posterior Pituitary Gland and the Female Reproductive Tract." In: The Pituitary Gland, G. W. HARRIS and B. T. DONOVAN (eds.), vol. 3. Berkeley, Univ. California Press, 1966, p. 453.

192. FITZPATRICK, R. J. "The Neurohypophysis and the Male Reproductive Tract." In: The Pituitary Gland, G. W. HARRIS and B. T. DONOVAN (eds.), vol. 3. Berkeley, Univ. California Press, 1966, p. 505.

193. FITZSIMONS, J. T. The hypothalamus and drinking. Brit. Med. Bull. 22:232, 1966.

194. FLICKER, D. J. Pubertas praecox in a female infant caused by ventricular cyst; report of a case. J. Nerv. Ment. Dis. 98:42, 1943.

195. FOERSTER, O. Über Störungen der Thermoregulation bei Erkrankungen des Gehirns und Rückenmarks und bei Eingriffen am Zentralnervensystem. J. Psychiat. Neurol. 52:1, 1935.

196. FOERSTER, O. "Symptomatologie der Erkrankungen des Rückenmarks und seiner Wurzeln." In: Handbuch der Neurologie, O. BUMKE and O. FOERSTER (eds.), vol. 5. Berlin, Springer, 1936, p. 1.

197. FOERSTER, O., and GAGEL, O. Ein Fall von Ependymcyste des III. Ventrikels. Ein Beitrag zur Frage der Beziehungen psychischer Störungen zum Hirnstamm. Ztsch. ges. Neurol. Psychiat. 149:312, 1933.

198. FOERSTER, O., GAGEL, O., and MAHONEY, W. Vegetative Regulationen. Verhandl. dtsch. Gesellsch. inn. Med. 49:165, 1937.

199. FOG, M. General acquired anhidrosis. Report of a case and investigation of the heat regulation and circulation. J.A.M.A. 107:2040, 1936.

200. FRANÇOIS, J., and NEETENS, A. Oculomotor paralyses and tumors of the pituitary gland. Confin. Neurol. 30:239, 1968.

201. FREEMAN, F. R., AGNEW, H. W., and WILLIAMS, R. L. An electroencephalographic study of the effects of meprobamate on human sleep. Clin. Pharmacol. Ther. 6:172, 1965.

202. FREEMAN, W., and DUMOFF, E. Cerebellar syndrome following heat stroke. Arch. Neurol. Psychiat. 51:67, 1944.

203. FRENCH, J. D. "Corticofugal Connections with the Reticular Formation." In: Reticular Formation of the Brain, H. H. JASPER et al. (eds.). Boston, Little, Brown, 1958, p. 491.

204. FRENCH, J. D., HERNÁNDEZ-PEÓN, R., and LIVINGSTON, R. B. Projections from cortex to cephalic brain stem (reticular formation) in monkey. J. Neurophysiol. 18:74, 1955.

205. FRENCH, J. D., LONGMIRE, R. L., PORTER, R. W., and MOVIUS, H. J. Extravagal influences on gastric hydrochloric acid secretion induced by stress stimuli. Surgery 34:621, 1953.

206. FRENCH, J. D., PORTER, R. W., CAVANAUGH, E. B., and LONGMIRE, R. L. Experimental observations on "psychosomatic" mechanisms: Gastrointestinal disturbances. Arch. Neurol. Psychiat. 72:267, 1954.

207. FRENCH, J. D., VERZEANO, M., and MAGOUN, H. W. An extralemniscal sensory system in the brain. A.M.A. Arch. Neurol. Psychiat. 69:505, 1953.

208. FROHMAN, L. A., ACETO, T., Jr., and MacGILLIVRAY, M. H. Studies of growth hormone secretion in children: Normal, hypopituitary and constitutionally delayed. J. Clin. Endocrinol. 27:1409, 1967.

209. FULTON, J. F., and BAILEY, P. Tumors in the region of the third ventricle: Their diagnosis and relation to pathological sleep. J. Nerv. Ment. Dis. 69:1, 1929.

210. FULTON, J. F., LIVINGSTON, R. B., and DAVIS, G. D. Ablation of area 13 in primates. Fed. Proc. 6:108, 1947.

211. FUTCHER, T. B. A clinical report of nine cases of diabetes insipidus. Trans. Assn. Amer. Physicians 19:247, 1904.

212. FUXE, K. Cellular localization of monoamines in the median eminence and the infundibular stem of some mammals. Ztschr. Zellforsch. 61:710, 1964.

213. FUXE, K. Evidence for the Existence of Monoamine Neurons in the Central Nervous System. Uppsala, Almqvist & Wiksells, 1965.

214. FUXE, K., and HÖKFELT, T. "The Influence of Catecholamine Neurons on the Hormone Secretion from Anterior and Posterior Pituitary." In: Neurosecretion, F. STUTINSKY (ed.). Berlin, Springer, 1967, p. 165.

215. GABRIEL, P. Les pinéalomes (étude anatomo-clinique). Paris, Maloine, 1935.

216. GAGEL, O. "Symptomatologie der Erkrankungen des Hypothalamus." In: Handbuch der Neurologie, O. BUMKE and O. FOERSTER (eds.), vol. 5. Berlin, Springer, 1936, p. 482.

217. GALLINEK, A. Syndrome of episodes of hypersomnia, bulimia and abnormal mental states. J.A.M.A. 154:1081, 1954.

218. GARCIA, J. F., and GESCHWIND, I. I. "Investigation of Growth Hormone Secretion in Selected Mammalian Species." In: Growth Hormone, A. PECILE and E. E. MÜLLER (eds.). Amsterdam, Exc. Med. Found., Internat. Congr. Ser. No. 158, 1968, p. 276.

219. GAUPP, V., and SPATZ, H. Hypophysenstieldurchtrennung und Geschlechtsreifung. Über Regenerationserscheinungen an der suprasellären Hypophyse. Acta Neuroveg. 12:285, 1955.

220. GESCHWIND, N. Disconnexion syndromes in animals and man. Brain 88:237, 585, 1965.

221. GHATAK, N. R., HIRANO, A., and ZIMMERMAN, H. M. Intrasellar germinomas: A form of ectopic pinealoma. J. Neurosurg. 31:670, 1969.

222. GILBERT, G. J. Periodic hypersomnia and bulimia. Neurology 14:844, 1964.

223. GLICK, S. M., ROTH, J., YALOW, R. S., and BERSON, S. A. The regulation of growth hormone secretion. Recent Progr. Hormone Res. 21:241, 1965.

224. GOLD, E. M., KENT, J. R., and FORSHAM, P. H. Clinical use of a new diagnostic agent, methopyrapone (SU-4885), in pituitary and adrenocortical disorders. Ann. Int. Med. 54:175, 1961.

225. GOLD, J. Development of heat pyrexia. J.A.M.A. 173:1175, 1960.

226. GOLDMAN, K. P., and JACOBS, A. Anterior and posterior pituitary failure after head injury. Brit. Med. J. 2:1924, 1960.

227. GOODMAN, L. S., and GILMAN, A. The Pharmacological Basis of Therapeutics, 3d edit. New York, Macmillan, 1965, p. 868.

228. GOODSITT, A. Anorexia nervosa. Brit. J. Med. Psychol. 42:109, 1969.

229. GOTTSCHALK, P. G., and THOMAS, J. E. Heat stroke. Mayo Clin. Proc. 41:470, 1966.

230. GREEN, J. D. "Neural Pathways to the Hypophysis." In: Hypothalamic-Hypophysial Interrelationships, W. S. FIELDS et al. (eds.). Springfield, Thomas, p. 3.

231. GREEN, J. D. "The Rhinencephalon and Behavior." In: Neurological Basis of Behavior, G. E. W. WOLSTENHOLME and C. M. O'CONNOR (eds.). Ciba Found. Sympos. Boston, Little, Brown, 1958, p. 222.

232. GREEN, J. D. "Neural Pathways to the Hypophysis: Anatomical and Functional." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 276.

233. GREEN, J. D., and HARRIS, G. W. The neurovascular link between the neurohypophysis and adenohypophysis. J. Endocrinol. 5:136, 1947.

234. GRESHAM, S. C., AGNEW, H. W., and WILLIAMS, R. L. The sleep of depressed patients. Arch. Gen. Psychiat. 13:503, 1965.

235. GREEN, J. R., BUCHAN, G. C., ALVORD, E. C., Jr., and SWANSON, A. G. Hereditary and idiopathic types of diabetes insipidus. Brain 90:707, 1967.

236. GREEN, L. N., and CRACCO, R. Q. Kleine-Levin syndrome. A case with EEG evidence of periodic brain dysfunction. Arch. Neurol. 22:166, 1970.

237. GREENBERG, R., and PEARLMAN, C. Delirium tremens and dreaming. Amer. J. Psychiat. 124:133, 1967.

238. GREEP, R. O. Functional pituitary grafts in rats. Proc. Soc. Exp. Biol. Med. 34:754, 1936.

239. GREER, M. A. Studies on the influence of the central nervous system on anterior pituitary function. Recent Progr. Hormone Res. 13:67, 1957.

240. GREGERSON, M. I., and RAWSON, R. A. Blood volume. Physiol. Rev. 39:307, 1959.

241. GROSS, M. M., GOODENOUGH, D., TOBIN, M., HALPERT, E., LEPORE, D., et al. Sleep disturbances and hallucinations in acute alcoholic psychosis. J. Nerv. Ment. Dis. 142:493, 1966.

242. GROSSMAN, S. P. "Some Neurochemical Aspects of Central Regulation of Thirst." In: Thirst, M. J. WAYNER, (ed.). Oxford, Pergamon, 1964, p. 487.

243. GRÜNTHAL, E. Über das spezifisch Menschliche im Hypothalamusbau. Psychol. Neurol. 45:237, 1933.

244. GUILLERY, R. W. A quantitative study of the mammillary bodies and their connexions. J. Anat. 89:19, 1955.

245. HABENER, J. F., and DASHE, A. M. Hypothalamic change and water metabolism following Yttrium, Y 99 hypophysectomy in man. Arch. Neurol. Psychiat. 12:177, 1966.

246. HALL, W. H., and SMITH, G. P. Gastric secretory response to chronic hypothalamic stimulation in monkeys. Gastroenterology 57:491, 1969.

247. HALL, R., ANDERSON, J., and SMART, G. A. Clinical Endocrinology. Philadelphia, Lippincott, 1969, p. 388.

248. HAMMEL, H. T. Regulation of internal body temperature. Ann. Rev. Physiol. 30:641, 1968.

249. HANKISS, J., KESZTHELYI, M., and SIRO, B. A new type of diabetes insipidus due to increased hormone inactivation: Its incidence in clinical material. Amer. J. Med. Sci. 242:605, 1961.

250. HARDAWAY, R. M. Syndromes of Disseminated Intravascular Coagulation with Special Reference to Shock and Hemorrhage. Springfield, Thomas, 1966.

251. HARDY, J. D., HELLON, R. F., and SUTHERLAND, K. Temperature-sensitive neurones in the dog's hypothalamus. J. Physiol. 175:242, 1964.

252. HARLIN, R. S., and GIVENS, J. R. Sheehan's syndrome associated with eclampsia and a small sella turcica. South. Med. J. 61:909, 1968.

253. HARRIS, G. W. Neural Control of the Pituitary Gland. London, Arnold, 1955, p. 7.

254. HARRIS, G. W., and JACOBSOHN, D. Functional grafts of anterior pituitary gland. Proc. Roy. Soc., B 139:263, 1952.

255. HARRIS, G. W., and WOODS, J. W. Electrical stimulation of the hypothalamus and thyroid activity. Nature 178:80, 1956.

256. HAYMAKER, W. "Blood Supply of the Human Hypothalamus." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 210.

257. HAYMAKER, W. Bing's Local Diagnosis in Neurological Diseases. 15th ed., 1st reprinting. St. Louis, Mosby, 1969.

258. HAYMAKER, W., and ANDERSON, E. The syndromes arising from hyperfunction of the adrenal cortex: The adrenogenital and Cushing's syndromes - a review. Internat. Clin. n.s. 4:245, 1938.

259. HAYWARD, J. N. Brain temperature and thermosensitivity of nerve cells in monkey. Trans. Amer. Neurol. Assn. 94:157, 1969.

260. HEATH, R. G. Studies in Schizophrenia. A Multidisciplinary Approach to Mind-Brain Relationships. Cambridge, Harvard Univ. Press, 1954.

261. HENDERSON, W. R. The pituitary-adenomata. A follow-up study of surgical results in 338 cases. (Dr. Harvey Cushing's series.) Brit. J. Surg. 26:811, 1939.

262. HENRY, J. P., GAUER, O. H., and REEVES, J. L. Evidence of the atria location of receptors influencing urine flow. Circulation Res. 4:85, 1956.

263. HERRICK, C. J. The amphibian forebrain. IV. Necturus. J. Comp. Neurol. 58:1, 1933.

264. HESS, W. R. Das Schlafsyndrom als Folge dienzephaler Reizung. Helv. Physiol. Pharmacol. Acta 2:305, 1944.

265. HESS, W. R. "The Diencephalic Sleep Centre." In: Brain Mechanisms and Consciousness, J. F. DELAFRESNAYE (ed.). Springfield, Thomas, 1954, p. 117.

266. HESS, W. R. Die funktionelle Organisation des vegetativen Nervensystems. Basel, Schwabe, 1948, p. 140.

267. HESS, W. R. Diencephalon Autonomic and Extrapyramidal Functions. New York, Grune & Stratton, 1954, pp. 14, 16, 17, 25.

268. HESS, W. R., and BRÜGGER, M. Das subkorticale Zentrum der affektiven Abwehrreaktion. Helv. Physiol. Pharmacol. Acta 1:33, 1943.

269. HETHERINGTON, A. W. The production of hypothalamic obesity in rats already displaying chronic hypopituitarism. Amer. J. Physiol. 140:89, 1943.

270. HETHERINGTON, A. W., and RANSON, S. W. The relation of various hypothalamic lesions to adiposity in the rat. J. Comp. Neurol. 76:475, 1942.

271. HICKEY, R. C., and HARE, K. The renal excretion of chloride and water in diabetes insipidus. J. Clin. Invest. 23:768, 1944.

272. HODES, R., and DEMENT, W. C. Depression of electrically induced reflexes (H-reflexes) in man during low voltage EEG 'sleep.' EEG Clin. Neurophysiol. 17:617, 1964.

273. HOFF, F. Summary and conclusion from the internal medical aspect. Progr. Brain Res. 18:244, 1965,

273a. HSIEH, A. C. L., and CARLSON, L. D. Role of the thyroid in metabolic response to low temperature. Amer. J. Physiol. 188:40, 1957.

274. HUNSPERGER, R. W. Affektreaktionen auf elektrische Reizung im Hirnstamm der Katze. Helv. Physiol. Acta 14:70, 1956.

275. IFFT, J. D. Evidence of gonadotropic activity of the hypothalamic arcuate nucleus in the female rat. Anat. Rec. 142:1, 1962.

276. IFFT, J. D. The effect of endocrine gland extirpations on the size of nucleoli on rat hypothalamic neurons. Anat. Rec. 148:599, 1964.

277. IGGO, A. Temperature discrimination in the skin. Nature 204:481, 1964.

278. INGRAM, W. R. The hypothalamus: A review of the experimental data. Psychosom. Med. 1:48, 1939.

279. INGRAM, W. R., and BARRIS, R. W. Evidence of altered carbohydrate metabolism in cats with hypothalamic lesions. Amer. J. Physiol. 114:562, 1936.

280. INGRAM, W. R., BARRIS, R. W., and RANSON, S. W. Catalepsy. An experimental study. Arch. Neurol. Psychiat. 35:1175, 1936.

281. ISHIKAWA, I., KOIZUMI, K., and BROOKS, C. McC. Electrical activity recorded from the pituitary stalk of the cat. Amer. J. Physiol. 210:427, 1966.

282. ISHIKAWA, K., OTT, K., ELDRED, E., and STUART, D. Response of motoneurons to hypothalamic stimulation and its relation to thermoregulatory behavior. Amer. J. Phys. Med. 46:1290, 1967.

283. IVY, H. K. The syndrome of inappropriate secretion of antidiuretic hormone. Med. Clin. N. Amer. 52:817, 1968.

284. JACKSON, I. M. D., WHYTE, W. G., and GARREY, M. M. Pituitary function following uncomplicated pregnancy in Sheehan's syndrome. J. Clin. Endocrinol. Metab. 29:315, 1969.

285. JACOBSON, A., KALES, A., LEHMANN, D., and HOEDEMAKER, F. S. Muscle tonus in human subjects during sleep and dreaming. Exp. Neurol. 10:418, 1964.

286. JACOBSON, A., KALES, A., LEHMANN, D., and ZWEIZIG, J. R. Somnambulism; all-night electroencephalographic studies. Science 148:975,1965.

287. JASPER, H. H. "Recent Advances in Our Understanding of Ascending Activities of the Reticular System." In: Reticular Formation of the Brain, H. H. JASPER et al. (eds.). Boston, Little, Brown, 1958, p. 319.

288. JEFFERSON, G. "The Invasive Adenomas of the Anterior Pituitary." In: The Sherrington Lectures, vol. 3. Liverpool, Univ. Press of Liverpool, 1955, p. 63.

289. JENKINS, J. S., and ELSE, W. Pituitary-adrenal function tests in patients with untreated pituitary tumours. Lancet 2:940, 1968.

290. JEWELL, P. A., and VERNEY, E. B. An experimental attempt to determine the site of the neurohypophysial receptors in the dog. Phil. Trans. Roy. Soc., B 240:197, 1957.

291. JOHNSTON, C. I., and DAVIES, J. O. Evidence from cross circulation studies for a humoral mechanism in the natriuresis of saline loading. Proc. Soc. Exp. Biol. Med. 121:1058, 1966.

292. JONES, N. F., BARRACLOUGH, M. A., and MILLS, I. H. The mechanism of increased sodium excretion during water loading with 2.5% dextrose and vasopressin. Clin. Sci. 25:449, 1963.

293. JOUVET, M. Paradoxical sleep - a study of its nature and mechanisms. Progr. Brain Res. 18:20, 1965.

294. JOUVET, M., and DELORME, E. Locus coeruleus et sommeil paradoxal. C. R. Soc. Biol. 154:895, 1965.

295. JUNG, R., and KUHLO, W. Neurophysiological studies of abnormal night sleep and the Pickwickian syndrome. Progr. Brain Res. 18:140, 1965.

296. KABAT, H., ANSON, B. J., MAGOUN, H. W., and RANSON, S. W. Stimulation of the hypothalamus with special reference to its effect on gastrointestinal motility. Amer. J. Physiol. 112:214, 1935.

297. KAHLE, W. Zur Entwicklung des menschlichen Zwischenhirnes. Dtsch. Ztschr. Nervenheilk. 175:259, 1956.

298. KAHLE, W. "Über die längszonale Gliederung des menschlichen Zwischenhirnes." In: Pathophysiologia Diencephalica, S. B. CURRI, L. MARTINI and W. KOVAC (eds.). Vienna, Springer, 1958, p. 134.

299. KAHN, E. A. Some physiologic implications of craniopharyngiomas. Neurology 9:82, 1959.

300. KAJIHARA, A., and KENDALL, J. W. Studies on the hypothalamic control of TSH secretion. Neuroendocrinology 5:53, 1969.

301. KALES, A., JACOBSON, A., PAULSON, M. J., KALES, J. D., and WALTER, R. D. Somnambulism: Psychophysiological correlates. Arch. Gen. Psychiat. 14:586, 1966.

302. KAPLAN, N. M. Assessment of pituitary ACTH secretary activity capacity with Metopirone. 1. Interpretation. J. Clin. Endocrinol. 23:945, 1963.

303. KELLER, A. D. Ulceration in the digestive tract of the dog following intracranial procedures. Arch. Path. 21:127, 165, 1936.

304. KELLER, A. D. The role of circulation in the physiology of heat regulation. Physical Ther. Rev. 30:1, 1950.

305. KENDALL, J. W. Studies on the inhibition of corticotropin and thyrotropin release utilizing microinjections into the pituitary. Endocrinology 71:452, 1962.

306. KENNAWAY, E. L., and MOTTRAM, J. C. Observations upon two cases of diabetes insipidus, with an account of the literature relating to an association between the pituitary gland and this disease. Quart. J. Med. 12:225, 1919.

307. KENNEDY, G. C. Food intake, energy balance and growth. Brit. Med. Bull. 22:216, 1966.

308. KINGSBURY, B. F. The fundamental plan of the vertebrate brain. J. Comp. Neurol. 34:461, 1922.

309. KINGSBURY, B. F. The developmental significance of the floorplate of the brain and spinal cord. J. Comp. Neurol. 50:177, 1930.

310. KLEEMAN, C. R., and FICHMAN, M. P. The clinical physiology of water metabolism. New Engl. J. Med. 277:1300, 1967.

311. KLEITMAN, N. Sleep and Wakefulness, 2nd ed. Chicago, Univ. Chicago Press, 1963.

312. KLÜVER, H., and BARTELMEZ, G. W. Endometriosis in a rhesus monkey. Surg. Gynec. Obst. 92:650, 1951.

313. KLÜVER, H., and BUCY, P. C. Preliminary analysis of functions of the temporal lobes in monkeys. Arch. Neurol. Psychiat. 42:979, 1939.

314. KNOBIL, E., and MEYER, V. Observations on the secretion of growth hormone, and its blockage, in the rhesus monkey. Ann. N. Y. Acad. Sci. 148:459, 1968.

315. KNOBIL, E., MEYER, V., and SCHALLY, A. V. "Hypothalamic Extracts and the Secretion of Growth Hormone in the Rhesus Monkey." In: Growth Hormone, A. PECILE and E. E. MULLER (eds.). Amsterdam, Exc. Med. Found., Internat. Congr. Ser. No. 158, 1968, p. 226.

316. KNOWLES, F. "Neuronal Properties of Neurosecretory Cells." In: Neurosecretion, F. Stutinsky (ed.). Berlin, Springer, 1967, p. 8.

317. KOBAYASHI, H., OOTA, Y., UEMURA, H., and HIRANO, T. Electron microscopic and pharmacological studies on the rat median eminence. Ztschr. Zellforsch. 71:387, 1966.

318. KOBURN, J. W., and REBA, R. C. Potassium depletion in heat stroke: A possible etiological factor. Mil. Med. 131:678, 1966.

319. KOELLA, W. P. Sleep, its Nature and Physiological Organization. Springfield, Thomas, 1967.

320. KOELLA, W. P. "The Central Nervous Control of Sleep." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 622.

321. KOIKEGAMI, H., YAMADA, T., and USUI, K. Stimulation of amygdaloid nuclei and periamygdaloid cortex with special reference to its effect on uterine movements and ovulation. Folia Psychiat. Neurol. Jap. 8:7, 1954.

322. KONNAK, J. W., and CERNY, J. C. The surgical treatment of Cushing's disease. J. Urol. 102:653, 1969.

323. KORNBLUM, R. N., and FISHER, R. S. Pituitary lesions in craniocerebral injuries. Arch. Path. 88:242, 1969.

324. KOVÁCS, K. Necrosis of the anterior pituitary in humans. Neuroendocrinology 4:170, 201, 1969.

325. KUHLENBECK, H. Bemerkungen über den Zwischenhirnbauplan bei Säugetieren, insbesondere beim Menschen. Anat. Anz. 70:122, 1930.

326. KUHLENBECK, H. The derivatives of the thalamus ventralis in the human brain and their relation to the so-called subthalamus. Mil. Surgeon 102:433, 1948.

327. KUHLENBECK, H. The Human Diencephalon. A Summary of Development, Structure, Function, and Pathology. Basel, Karger, 1954, pp. 9, 13, 28.

328. KUHLENBECK, H., and HAYMAKER, W. The derivatives of the hypothalamus in the human brain; their relation to the extrapyramidal and autonomic systems. Mil. Surgeon 105:26, 1949.

329. KUNO, Y. Human Perspiration. Thomas, Springfield, 1945.

330. KUYPERS, H. G. J. M., and LAWRENCE, D. G. Cortical projections to the red nucleus and the brain stem in the Rhesus monkey. Brain Res. 4:151, 1967.

331. LADELL, W. S. S., WATERLOW, J. C., and HUDSON, M. F. Desert climate. Physiological and clinical observations. Lancet 2:491, 527, 1944.

332. LANGE-COSACK, H. Verschiedene Gruppen der hypothalamischen Pubertas praecox. Dtsch. Ztschr. Nervenheilk. 166:499, 1951.

333. LAQUEUR, G. L., McCANN, S. M., SCHREINER, L. H., ROSEMBERG, E., RIOCH, D. McK., and ANDERSON, E. Alterations of adrenal cortical and ovarian activity following hypothalamic lesions. Endocrinology 57:44, 1955.

334. LEAF, A., BARTTNER, F. C., SANTOS, R. F., and WRONG, O. Evidence in man that urinary electrolyte loss induced by pitressin is function of water retention. J. Clin. Invest. 32:868, 1953.

335. LEE, J. "Neurohypophyseal Hormones. Their Role in Oedema of Man, with Reference to their Action on the Alimentary Canal and on Metabolism." In: The Pituitary Gland, G. W. HARRIS and B. T. DONOVAN (eds.), vol. 3. Berkeley, Univ. California Press, 1966, p. 517.

336. Le GASSICKE, J., ASHCROFT, G. W., ECCLESTON, D., EVANS, J. I., OSWALD, I., and RITSON, E. B. The clinical state, sleep and tranylcypromine ("Parmate") addict. Brit. J. Psychiat. 111:357, 1965.

337. LEITHEAD, C. S., GUTHRIE, J., De La PLACE, S., and MAEGRAITH, B. Incidence, aetiology, and prevention of heat illness on ships in the Persian Gulf. Lancet 2:109, 1958.

338. LEITHEAD, C. S., and PALLISTER, M. A. Observations on dehydration and sweating. Lancet 2:114, 1960.

339. Le MARQUAND, H. S., and RUSSELL, D. S. A case of pubertas praecox (macrogenitosomia praecox) in a boy associated with a tumour in the floor of the third ventricle. Roy. Berkshire Hosp. Rep. 1934-35, p. 31.

340. LEVEQUE, T. F. Changes in the neurosecretory cells of the rat hypophysis following ingestion of sodium chloride. Anat. Rec. 117:741, 1953.

341. LEVIN, M. Narcolepsy (Gélineau's syndrome) and other varieties of morbid somnolence. Arch. Neurol. Psychiat. 22:1172, 1929.

342. LEZNOFF, A., FISHMAN, J., GOODFRIEND, L., McGARRY, E., BECK, J., and ROSE, B. Localization of fluorescent antibodies to human growth hormone in human pituitary glands. Proc. Soc. Exp. Biol. Med. 104:232, 1960.

343. LI, C. H. "The Chemistry of Human Pituitary Growth Hormone: 1956-1966." In: Growth Hormone, A. PECILE and E. E. MULLER (eds.). Amsterdam, Exc. Med., Found., Internat. Congr. Ser. No. 158, 1968, p. 3.

344. LICHARDUS, B., and PIERCE, J. W. Evidence for a humoral natriuretic factor released by blood volume expansion. Nature 209:407, 1966.

345. LIDDLE, G. W. Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. J. Clin. Endocrinol. 20:1539, 1960.

346. LIDDLE, G. W., ISLAND, D., and MEADOR, C. K. Normal and abnormal regulation of corticotrophin secretion in man. Recent Progr. Hormone Res. 18:125, 1962.

347. LIPSETT, A. B., DREIFUSS, F. E., and THOMAS, L. D. Hypothalamic syndrome following varicella. Amer. J. Med. 32:471, 1962.

348. LIPSMEYER, E., and ACKERMAN, G. L. Irreversible brain damage after water intoxication. J.A.M.A. 196:286, 1966.

349. LISK, R. D. "The Hypothalamus and Hormone Sensory Systems." In: Hormonal Steroids. Exc. Med. Found., Internat. Congr. Ser. No. 132, 1967, p. 952.

350. LIVINGSTON, R. B., FULTON, J. R., DELGADO, J. M. R., SACHS, E., Jr., BRENDLER, S. J., and DAVIS, G. D. Stimulation and regional ablation of orbital surface of frontal lobe. A. Res. Nerv. Ment. Dis., Proc. 27:405, 1948.

351. LLŌYD, C. W. "Central Nervous System Regulation of Endocrine Function in the Human." In: Advances in Neuroendocrinology, A. W. NALBANDOV (ed.). Urbana, Univ. Illinois Press, 1963, p. 460.

352. LOMBARDI, G. Radiology in Neuro-ophthalmology. Baltimore, Williams & Wilkins, 1967.

353. LORIDAN, L., and SENIOR, B. Cushing's syndrome in infancy. J. Ped. 75:349, 1969.

354. LUBAR, J. F., SCHAEFER, C. F., and WELLS, D. G. The role of the septal area in the regulation of water intake and associated motivational behavior. Ann. N. Y. Acad. Sci. 157:531, 1969.

355. LUNDBAEK, K., MALMROS, R., and MOGENSEN, E. F. The effect of pituitary stalk section in man. Acta Med. Scandinav. 166:9, 1960.

356. LUNDBERG, P. O. A study of neurosecretory and related phenomena in the hypothalamus and pituitary of man. Acta Morph. Neerl.-Scandinav. 1:256, 1957.

357. LUNDBERG, P. O., and GEMZELL, C. Dysplasia of the sella turcica: Clinical and laboratory investigations in three cases. Acta Endocrinol. 52:478, 1966.

358. LUNDBERG, P. O., and HUGOSSON, R. Application of the Metopirone test to tumors in the region of the sella turcica. J. Neurosurg. 25:543, 1966.

359. LUNDBERG, P. O., and WIDE, L. Vasopressin test in tumours of the sellar region. Neuroendocrinology 5:64, 1969.

360. MACCUBBIN, D. A., and VAN BUREN, J. M. A quantitative evaluation of hypothalamic degeneration and its relation to diabetes insipidus following interruption of the human hypophysial stalk. Brain 86:443, 1963.

361. MacLEAN, P. D. The limbic system and its hippocampal formation. Studies in animals and their possible application to man. J. Neurosurg. 11:29, 1954.

362. MacLEAN, P. D. Limbic system ("visceral brain") in relation to central gray and reticulum of brain stem. Psychosomat. Med. 17:355, 1955.

363. MacLEAN, P. D. Chemical and electrical stimulation of hippocampus in unrestrained animals. II. Behavioral findings. A.M.A. Arch. Neurol. Psychiat. 78:128, 1957.

364. MacLEAN, P. D. Contrasting functions of limbic and neocortical systems of the brain and their relevance to psychophysiological aspects of medicine. Amer. J. Med. 25:611, 1958.

365. MacLEAN, P. D. "The Hypothalamus and Emotional Behavior." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 659.

366. MAGOUN, H. W. "The Ascending Reticular System and Wakefulness." In: Brain Mechanisms and Consciousness, J. F. DELAFRESNAYE (ed.). Springfield, Thomas, 1954, p. 1.

367. MAGOUN, H. W. The Waking Brain. Springfield, Thomas, 1958.

368. MALAMUD, N., HAYMAKER, W., and CUSTER, R. P. Heat stroke. A clinico-pathologic study of 125 fatal cases. Mil. Surgeon 99:397, 1946.

369. MARK, V. H., SMITH, J. L., and KJELLBERG, R. D. Suprasellar epidermoid tumor. A case report with the presenting complaint of see-saw nystagmus. Neurology 10:81, 1960.

370. MARTIN, F. I. R. Familial diabetes insipidus. Quart. J. Med., n.s. 28:573, 1959.

371. MASON, J. W. "The Central Nervous System Regulation of ACTH Secretion." In: Reticular Formation of the Brain, H. H. JASPER et al. (eds.). Boston, Little, Brown, 1958, p. 645.

372. MATSUI, N., and PLAGER, J. E. Rate of blood glucose fall as determinant factor in insulin-induced adrenocortical stimulation. Endocrinology 79:737, 1966.

373. MAYER, J. Some aspects of the problems of regulation of food intake and obesity. New Engl. J. Med. 274:662, 1966.

374. McCANN, S. M. Effect of hypothalamic lesions on the adrenal cortical response to stress in the rat. Amer. J. Physiol. 175:13, 1953.

374a. McCONNELL, E. M. The arterial blood supply of the human hypophysis cerebri. Anat. Rec. 115:175, 1953.

375. McGUIRE, J. L., and LISK, R. D. Localization of estrogen receptors in the rat hypothalamus. Neuroendocrinology 4:289, 1969.

376. McGHIE, A. The subjective assessment of sleep patterns in psychiatric illnesses. Brit. J. Med. Psychol. 39:221, 1966.

377. MEHTA, A. C., and BAKER, R. N. Persistent neurological deficits in heat stroke. Neurology 20:336, 1970.

378. MEISSNER, W. W. Memory function in the Korsakoff Syndrome. J. Nerv. Ment. Dis. 145:106, 1967.

379. MELCHIONNA, R. H., and MOORE, R. A. Pharyngeal pituitary gland. Amer. J. Path. 14:763, 1938.

380. MENDELS, J., and HAWKINS, D. R. Sleep and depression: A controlled EEG study. Arch. Gen. Psychiat. 16:344, 1967.

381. MESSIMY, R., NAMIN, P., and MARTINÈS, N. Tumeur kystique de l'hypophyse de type vésiculaire, a revêtement cilié. Rev. Neurol. 92:235, 1955.

382. METUZALS, J. "The Innervation of the Anterior Pituitary Gland in the Cat." In: Pathophysiologia Diencephalica, S. B. CURRI, L. MARTINI, and W. KOVAC (eds.). Vienna, Springer, 1958, p. 139.

383. MEYER, J. E. Pubertas praecox bei einer hyperplastischen Missbildung des Hypothalamus. Ein Beitrag zur Frage des Sexualzentrums und der Neurosekretion im Zwischenhirn. Arch. Psychiat. 179:378, 1948.

384. MILUNSKY, A., COWIE, V. A., and DONOGHUE, E. C. Cerebral gigantism in childhood. A report of two cases and a review of the literature. Pediatrics 40:395, 1967.

385. MONROE, L. J. Psychological and physiological differences between good and poor sleepers. J. Abnorm. Soc. Psychol. 72:255, 1967.

386. MONTREMURRO, D. G., and STEVENSON, J. A. F. Adipsia produced by hypothalamic lesions in the rat. Canad. J. Biochem. Physiol. 35:31, 1957.

387. MORAN, W. H., MILTENBERGER, F. W., SHUAYB, W. A., and ZIMMERMANN, B. The relationship of antidiuretic hormone secretion to surgical stress. Surgery 56:199, 1964.

388. MORGAN, L. O., and VONDERAHE, A. R. The hypothalamic nuclei in heat stroke. With notes on the central representation of temperature regulation. Arch. Neurol. Psychiat. 42:83, 1939.

389. MORGANE, P. J. The function of the limbic and rhinic forebrain-limbic midbrain systems and reticular formation in the regulation of food and water intake. Ann. N. Y. Acad. Sci. 157:806, 1969.

390. MORTON, A. A quantitative analysis of the normal neuron population of the hypothalamic magnocellular nuclei in man and of their projections to the neurohypophysis. J. Comp. Neurol. 136:143, 1969.

391. MORUZZI, G. Active processes in the brain stem during sleep. Harvey Lect. 58:233, 1962-63.

392. MORUZZI, G., and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. EEG Clin. Neurophysiol. 1:455, 1949.

393. MULLER, R., and WOHLFART, G. Craniopharyngiomas. Acta Med. Scandinav. 138:121, 1950.

394. MYERS, R. D. "Temperature Regulation: Neurochemical Systems in the Hypothalamus." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 506.

395. MYERS, R. D. Chemical mechanisms in the hypothalamus mediating eating and drinking in the monkey. Ann. N. Y. Acad. Sci. 157, 918, 1969.

396. MYERS, R. D., and YAKSH, T. L. Control of body temperature in the unanesthetized monkey by cholinergic and aminergic systems in the hypothalamus. J. Physiol. 202:483, 1969.

397. NAJJAR, S. S., and MAHMUD, J. Diabetes insipidus and diabetes mellitus in a six-year-old girl. J. Ped. 73:251, 1968.

398. NAKAYAMA, T., EISENMAN, J., and HARDY, J. D. Single unit activity of anterior hypothalamus during local heating. Science 134:560, 1961.

399. NAUTA, W. J. H. Hypothalamic regulation of sleep in rats. An experimental study. J. Neurophysiol. 9:285, 1946.

400. NAUTA, W. J. H. Hippocampal projections and related neural pathways to the mid-brain in the cat. Brain 81:319, 1958.

401. NAUTA, W. J. H. Neural associations of the amygdaloid complex in the monkey. Brain 85:505, 1962.

402. NAUTA, W. J. H., and HAYMAKER, W. "Hypothalamic Nuclei and Fiber Connections." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 136.

403. NAUTA, W. J. H., and KUYPERS, A. G. J. M. "Some Ascending Pathways in the Brain Stem Reticular Formation." In: Reticular Formation of the Brain, H. H. JASPER et al. (eds.). Boston, Little, Brown, 1958, p. 3.

404. NELSON, E., and HAYMAKER, W.: Colloid cyst of the third ventricle in flyers. Report of three fatal cases. J. Aviation Med. 28:356, 1957.

405. NETTER, F. H., and EZRIN, C. Hormones Produced by the Anterior Hypophysis. Ciba Clin. Sympos., vol. 15, no. 3, 1963.

406. NIEMER, W. T., and VONDERAHE, A. R. Cyst of the pulvinar of the thalamus; report of a case with obstructive internal hydrocephalus and diabetes mellitus of intermittent severity. Arch. Neurol. Psychiat. 44:1086, 1940.

407. NIKITOVITCH-WINER, M., and EVERETT, J. W. Functional restitution of pituitary grafts re-transplanted from kidney to median eminence. Endocrinology 63:916., 1958.

408. NORMAN, N., and VOGT, J. H. Oestrogen treatment in Cushing's syndrome. Acta Endocrinol. 61:320, 1969.

409. NORTHFIELD, D. W. C. Rathke-pouch tumours. Brain 80:293, 1957.

410. NORTHFIELD, D. W. C., and RUSSELL, D. S. Pubertas praecox due to hypothalamic hamartoma. Report of two cases surviving surgical removal of the tumour. J. Neurol. Neurosurg. Psychiat. 30:166, 1967.

411. NOWAKOWSKI, H. Infundibulum und Tuber cinereum der Katze. (Ein Beitrag zur Frage der Verknüpfung von Adenohypophyse und Hypothalamus bezüglich der Regulation der Sexualfunktionen.) Dtsch. Ztschr. Nervenheilk. 165:261, 1951.

412. O'BRIEN, C. P., Jr., and BACH, L. M. N. Observations concerning hypothalamic control of growth. Amer. J. Physiol. 218:226, 1970.

413. OLDS, J. Runway and maze behavior controlled by basomedial forebrain stimulation in the rat. J. Comp. Physiol. Psychol. 49:507, 1956.

414. OLDS, J. "Selective Effects of Drives and Drugs on 'Reward' Systems of the Brain." In: The Neurological Basis of Behaviour. Ciba Found. Sympos., London, Churchill, 1958, p. 124.

415. OLDS, J. Self-stimulation of the brain. Science 127:315, 1958.

416. OLDS, J., and MILNER, P. Positive reinforcement produced by electrical stimulation of septal areas and other regions of the rat brain. J. Comp. Physiol. Psychol. 47:419, 1954.

417. OLIVECRONA, H. Paraventricular nucleus and pituitary gland. Acta Physiol. Scandinav., (suppl. 136) 40:1, 1957.

418. OOMURA, Y., OOYAMA, H., YAMAMOTO, T., and NAKA, F. Reciprocal relationship of the lateral and ventromedial hypothalamus in the regulation of food intake. Physiol. Behav. 2:97, 1967.

419. OPPER, L., and ZIMMERMAN, H. M. Ulcers of the digestive tract in association with cerebral lesions. Yale J. Biol. Med. 11:49, 1938.

420. ORTHNER, H., and MEYER, E. Der posttraumatischen Diabetes insipidus. Befunde am neurosekretorischen System bei stumpfen Schädeltrauma, nebst Bemerkungen zum posttraumatischen Hirnödem. Acta Neuroveg. 30:216, 1967.

421. Reference deleted.

422. OSWALD, I. "Sleep and its Disorders." In: Handbook of Clinical Neurology, P. J. VINKEN and G. W. BRUYN (eds.), vol. 3. Amsterdam, North-Holland Publ. Co., 1969, p. 80.

423. OSWALD, I., BERGER, R. J., JARAMILLO, R. A., KEDDIE, K. M. G., OLLEY, P. C., and PLUNKETT, G. B. Melancholia and barbiturates: A controlled EEG, body and eye movement study of sleep. Brit. J. Psychiat. 109:66, 1963.

424. OSWALD, I., and PRIEST, R. G. Five weeks to escape the sleeping pill habit. Brit. Med. J. 2:1093, 1965.

425. OSWALD, I., and THACORE, V. R. Amphetamine and phenmetrazine addiction: Physiological abnormalities in the abstinence syndrome. Brit. Med. J. 2:427, 1963.

426. PADEL, Y., and DELL, P. Effets bulbaires et réticulaires des stimulations endormantes du tronc vago-aortique. J. Physiol. (Paris) 57:269, 1965.

427. PALAY, S. L. "The Fine Structure of the Neurohypophysis." In: Ultrastructure and Cellular Chemistry of Neural Tissue, H. WAELSCH (ed.), vol. 2. New York, Harper, 1957, p. 31.

428. PALEY, W. B., INSERILLO, A. J., and MALKARY, J. W. Puerperal diabetes insipidus and panhypopituitarism. Report of a case. Obst. Gynec. 34:96, 1969.

429. PALKOVITS, M., ZÁBORSZKY, L., and MAGYAR, P. Volume receptors in the diencephalon. Acta Morph. Acad. Sci. Hung. 16:391, 1968.

430. PAPEZ, J. W. A proposed mechanism of emotion. Arch. Neurol. Psychiat. 38:725, 1937.

431. PECHET, L. Fibrinolysis. New Engl. J. Med. 273:966, 1024, 1965.

432. PENFIELD, W. Diencephalic autonomic epilepsy. Arch. Neurol. Psychiat. 22:358, 1929.

433. PENFIELD, W., and FAULK, M. E. The insula. Further observations on its function. Brain 78:445, 1955.

434. PENFIELD, W., and JASPER, H. H. Epilepsy and the Functional Anatomy of the Human Brain. Boston, Little, Brown, 1954, pp. 27, 43, 107, 416.

435. PERRET, G. E. Stress ulcers and the neurosurgeon. J. Iowa Med. Soc. 54:583, 1964.

436. PICKFORD, M. "Neurohypophysis - Antidiuretic (Vasopressor) and Oxytocic Hormones." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 463.

437. PLEASURE, D. E., WALSH, G. O., and ENGEL, W. K. Atrophy of skeletal muscle in patients with Cushing's syndrome. Arch. Neurol. 22:118, 1970.

438. PORTER, R. J., and MILLER, R. A. Diabetes insipidus following closed head injury. J. Neurol. Neurosurg. Psychiat. 11:258, 1948.

439. PORTER, R. W., MOVIUS, H. J., and FRENCH, J. D. Hypothalamic influences on hydrochloric acid secretion of the stomach. Surgery 33:875, 1953.

440. PRADER, A., ZACHMANN, M., POLEY, J. R., ILLIG, R., and SZÉKY, J. "Studies with Human Growth Hormone in Hypopituitary Dwarfism." In: Growth Hormone, A. PECILE and E. E. MÜLLER (eds.). Amsterdam, Exc. Med. Found., Internat. Congr. Ser. No. 158, 1968, p. 388.

441. PRIBRAM, K. H. A review of theory in physiological psychology. Ann. Rev. Psychol. 11:1, 1960.

442. PRIBRAM, K. H., and BAGSHAW, M. Further analysis of the temporal lobe syndrome utilizing frontotemporal ablations. J. Comp. Neurol. 99:347, 1953.

443. PRIBRAM, K. H., and WEISKRANTZ, L. A comparison of the effects of medial and lateral cerebral resections on conditioned avoidance behavior in monkeys. J. Comp. Physiol. Psychol. 50:74, 1957.

444. PROCTOR, L. D., KNIGHTON, R. S., and CHURCHILL, J. A. Variations in consciousness produced by stimulating reticular formation of the monkey. Neurology 7:193, 1957.

445. PURVES, H. D. "Cytology of the Adenohypophysis." In: The Pituitary Gland, G. W. HARRIS and B. T. DONOVAN (eds.), vol. 1. Berkeley, Univ. California Press, 1966, p. 147.

446. RABEN, M. S. Human growth hormone. Recent Progr. Hormone Res. 15:71, 1959.

447. RABL, R. Die Variabilität des Nucleus paraformicalis des Menschen. Ztschr. Zellforsch. 65:116, 1965.

448. RAISMAN, G. The connexions of the septum. Brain 89:317, 1966.

449. RANSON, S. W. Somnolence caused by hypothalamic lesions in the monkey. Arch. Neurol. Psychiat. 41:1, 1939.

450. RANSON, S. W. Regulation of body temperature. A. Res. Nerv. Ment. Dis., Proc. 20:342, 1940.

451. RANSON, S. W., and INGRAM, W. R. Catalepsia caused by lesions between the mammillary bodies and the third nerve in the cat. Amer. J. Physiol. 101:690, 1932.

452. RANSON, S. W., and MAGOUN, H. W. The hypothalamus. Ergebn. Physiol. 41:56, 1939.

453. RASMUSSEN, A. T. Effects of hypophysectomy and hypophysial stalk resection on the hypothalamic nuclei of animals and man. A. Res. Nerv. Ment. Dis., Proc. 20:245, 1940.

454. RASMUSSEN, A. T., and GARDNER, W. J. Effects of hypophysial stalk resection on the hypophysis and hypothalamus of man. Endocrinology 27:219, 1940.

455. RECHTSCHAFFEN, A., and MARON, L. Effect of amphetamine on the sleep cycle. EEG Clin. Neurophysiol. 16:438, 1964.

456. REICHLIN, S. Editorial. Amer. J. Med. 43:477, 1967.

457. REICHLIN, S., and SCHALCH, D. S. "Growth Hormone Releasing Factor." In: Progress in Endocrinology, C. GUAL and F. J. G. EBLING (eds.). Amsterdam, Exc. Med. Found., Internat. Congr. Ser. No. 184, 1969, p. 584.

458. REYE, E. Die ersten klinischen Symptome bei Schwund des Hypophysenvorderlappens (Simmondsche Krankheit) und ihre erfolgreiche Behandlung. Dtsch. med. Wschr. 54:696, 1928.

459. RICHTER, E. Die Entwicklung des Globus pallidus und des Corpus subthalamicum. Berlin, Springer, 1965.

460. RICHTER, R. B. True hamartoma of the hypothalamus associated with pubertas praecox. J. Neuropath. Exp. Neurol. 10:368, 1951.

461. RICHTER, R. B., and TRAUT, E. F. Chronic encephalitis; pathological report of a case of protracted somnolence. Arch. Neurol. Psychiat. 44:848, 1940.

462. RIGGS, B. L., Jr., and RANDALL, R. V. Diabetes insipidus and diabetes mellitus: Report of case. Proc. Staff Meet. Mayo Clin. 35:30, 1960.

463. RIOCH, D., McK., WISLOCKI, G. B., and O'LEARY, J. L. A précis of preoptic, hypothalamic and hypophysial terminology with atlas. A. Res. Nerv. Ment. Dis., Proc. 20:3, 1940.

464. ROMEIS, B. "Innersekretorische Drüsen. II. Hypophyse." In: Handbuch der mikroscopischen Anatomie des Menschen, vol. 6, pt. 3, W. von MÖLLENDORFF (ed.). Berlin, Springer, 1940, pp. 389, 440.

465. ROMEO, J. A. Heatstroke. Mil. Med. 131:669, 1966.

466. ROSE, J. The cell structure of the mamillary body in mammals and in man. J. Anat. 74:91, 1939.

467. ROTH, B. Narkolepsie und Hypersomnie. Berlin, VEB Verlag Volk u. Gesundheit, 1962.

468. ROTH, J., GLICK, S. M., YALOW, B. S., and BERSON, S. A. Hypoglycemia: A potent stimulus to secretion of growth hormone. Science 140:987, 1963.

469. ROUTTENBERG, A., and MALSBURY, C. Brainstem pathways of reward. J. Comp. Physiol. Psychol. 68:22, 1969.

470. ROVIT, R. L., and BERRY, R. Cushing's syndrome and the hypophysis. A re-evaluation of pituitary tumors and hyperadrenalism. J. Neurosurg. 23:270, 1965.

471. ROVIT, R. L., and DUANE, T. D. Cushing's syndrome and pituitary tumors. Pathophysiology and ocular manifestations of ACTH-secreting pituitary adenomas. Amer. J. Med. 46:416, 1969.

472. ROWE, S. N. Localization of the sleep mechanism. Brain 58:21, 1935.

473. RUSCIO, J. F., and MARCUS, P. S. Sudden hyperthermia during anesthesia. Surg. Clin. N. Amer. 48:415, 1968.

474. RUSHTON, J. G. Sleep paralysis: Report of two cases. Proc. Staff Meet. Mayo Clin. 19:51, 1944.

475. RUSSELL, D. S. Effects of dividing the pituitary stalk in men. Lancet 1:466, 1956.

476. RUSSFIELD, A. B. "Diseases of the Pituitary." In: Pathology of the Nervous System," J. MINCKLER (ed.), vol. 1. New York, McGraw-Hill, 1968, p. 619.

477. RYDIN, H., and VERNEY, E. B. The inhibition of water diuresis by emotional stress and by muscular exercise. Quart. J. Exp. Physiol. 27:343, 1938.

478. SALASSA, R. M., KEARNS, T. P., KERNOHAN, J. W., SPRAGUE, R. G., and MacCARTHY, C. S. Pituitary tumors in patients with Cushing's syndrome. J. Clin. Endocrinol. 19:1523, 1959.

479. SALEM, S. N. Neurological complications of heat-stroke in Kuwait. Ann. Trop. Med. Parasitol. 60:393, 1966.

480. SANO, Y., ODAKE, G., and TAKETOMO, S. Fluorescence microscopic and electron microscopic observations on the tuberohypophysial tract. Neuroendocrinology 2:30, 1967.

481. SAWYER, C. H. "Regulatory Mechanisms of Secretion of Gonodotrophic Hormones." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 389.

482. SCHICKELE, E. Environment and fatal heat stroke. An analyses of 157 cases occurring in the Army in the U.S. during World War II. Mil. Surgeon 100:235, 1947.

483. SCHLEZINGER, N. S., and THOMPSON, R. A. Pituitary tumors with central scotomas simulating retrobulbar optic neuritis. Neurology 17:782, 1967.

484. SCHMIDT, E., HALLERVORDEN, J., and SPATZ, H. Die Entstehung der Hamartome am Hypothalamus mit und ohne Pubertas praecox. Dtsch. Ztschr. Nervenheilk. 177:235, 1958.

485. SCHREIBER, V. "Chemistry of Hypothalamic Releasing Factors." In: Progress in Endocrinology, C. GUAL and F. J. G. EBLING (eds.). Amsterdam, Exc. Med. Found., Internat. Congr. Ser. No. 184, 1969, p. 555.

486. SCHREINER, L., and KLING, A. Effects of castration on hypersexual behavior induced by rhinencephalic injury in cat. A.M.A. Arch. Neurol. Psychiat. 72:180, 1954.

487. SCHWARTZ, B. A., SEGUY, M., and ESCANDE, J. P. Correlations EEG, respiratoires, oculaires et myographiques dans le 'syndrome pickwickien' et autres affections paraissant apparentées: Proposition d'un hypothèse. Rev. Neurol. 117:145, 1967.

488. SEIP, M., van der HAGEN, C. B., and TRYGSTAD, O. Hereditary pituitary dwarfism with spontaneous puberty. Arch. Dis. Childh. 43:47, 1968.

489. SHANKLIN, W. H. Incidence and distribution of cilia in the human pituitary with a description of microfollicular cysts derived from Rathke's cleft. Acta Anat. Scandinav. 11:361, 1951.

490. SHARKEY, P. C., PERRY, J. H., and EHNI, G. Diabetes insipidus following section of the hypophyseal stalk. J. Neurosurg. 18:445, 1961.

491. SHARMA, K. N., ANAND, B. K., DUA, S., and SINGH, B. Role of the stomach in regulation of activities of hypothalamic feeding centers. Amer. J. Physiol. 201:593, 1961.

492. SHEEHAN, D. The hypothalamus and gastro-intestinal regulation. A. Res. Nerv. Ment. Dis., Proc. 20:589, 1940.

493. SHEEHAN, H. L. Atypical hypopituitarism. Proc. Roy. Soc. Med. 54:43, 1961.

494. SHEEHAN, H. L., and DAVIS, J. C. Pituitary necrosis. Brit. Med. Bull. 24:59, 1968.

495. SHEEHAN, H. L., and KOVÁCS, K. The subventricular nucleus. Brain 89:589, 1966.

496. SHEEHAN, H. L., and MURDOCH, R. Post-partum necrosis of the anterior pituitary; pathological and clinical aspects. J. Obst. Gynaec. Brit. Emp. 45:456, 1938.

497. SHEEHAN, H. L., and SUMMERS, V. K. The syndrome of hypopituitarism. Quart. J. Med. 18:319, 1949.

498. SHEEHAN, H. L., and WHITEHEAD, R. The neurohypophysis in postpartum hypopituitarism. J. Path. Bact. 85:145, 1963.

499. SIMMONDS, M. Über Hypophysisschwund mit tödlichem Ausgang. Dtsch. med. Wchnschr. 40:322, 1914.

500. SIMMONDS, M. A. Effect of environmental temperature on the turnover of noradrenaline in hypothalamus and other areas of the rat brain. J. Physiol. 203:199, 1969.

501. SIMPSON, L. R., LAMPE, I., and ABELL, M. R. Suprasellar germinomas. Cancer 22:533, 1968.

502. SINHA, S. N. Thiazide treatment of diabetes insipidus. Practitioner 203:674, 1969.

503. SJÖQVIST, O. Hypothalamic discharge and its relation to epilepsy. With the report of a case of "sham rage" in man with surgical verification. Acta Chir. Scandinav. 85:235, 1941.

504. SLOPER, J. C. The application of newer histochemical and isotope techniques for the localisation of protein-bound cystine or cysteine to the study of hypothalamic neurosecretion in normal and pathological conditions. 2d Internat. Sympos. Neurosecretion, Lund, 1957, p. 20.

505. SLOPER, J. C. Hypothalamo-neurohypophysial neurosecretion. Internat. Rev. Cytology 7:337, 1958.

506. SLOPER, J. C. The presence of posterior pituitary-like structures in the hypothalamus after hypophysectomy: Observations on 20 human subjects. (Abst.) Proc. 1st Internat. Endocrine Congr., Copenhagen, 1960.

507. SLOPER, J. C. Hypothalamic neurosecretion. The validity of the concept of neurosecretion and its physiological and pathological implications. Brit. Med. Bull. 22:209, 1966.

508. SLOPER, J. C. "The Experimental and Cytopathological Investigation of Neurosecretion in the Hypothalamus and Pituitary." In: The Pituitary Gland, G. W. HARRIS and B. T. DONOVAN (eds.), vol. 3, Berkeley, Univ. California Press, 1966, p. 131.

509. SLOPER, J. C., and ADAMS, C. W. M. The hypothalamic elaboration of posterior pituitary principle in man. Evidence derived from hypophysectomy. J. Path. Bact. 72:587, 1956.

510. SMITH, K. R., Jr., WEINBERG, W. A., and McALISTER, W. H. Failure to thrive. The diencephalic syndrome of infancy and childhood; a case report. J. Neurosurg. 23:348, 1965.

511. SMITH, P. E. The disabilities caused by hypophysectomy and their repair. J.A.M.A. 88:158, 1927.

512. SMITH, R. W., and McCANN, S. Aphagia, adipsia and polydipsia following hypothalamic lesions in the rat. Fed. Proc. 20:333, 1961.

513. SOHAL, R. S., SUN, S. C., COLCOLOUGH, H. L., and BURCH, G. E. Heat stroke. An electron microscopic study of endothelial cell damage and disseminated intravascular coagulation. Arch. Int. Med. 122:43, 1968.

514. SOKOL, H. W., and VALTIN, H. Evidence for the synthesis of oxytocin and vasopressin in separate neurons. Nature 214:314, 1967.

515. SOURS, J. A. Narcolepsy and other disturbances in the sleep-waking rhythm: A study of 115 cases with review of the literature. J. Nerv. Ment. Dis. 137:525, 1963.

516. SPATZ, H. Über Gegensätzlichkeit und Verknüpfung bei der Entwicklung von Zwischenhirn und "Basaler Rinde." Allg. Ztschr. Psychiat. 125:166, 1949.

517. SPATZ, H. Neues über die Verknupfung von Hypophyse und Hypothalamus. Mit besonderer Berücksichtigung der Regulation sexueller Leistungen. Acta Neuroveg. 3:5, 1951.

518. SPATZ, H. "Die Proximale (supraselläre) Hypophyse, ihre Beziehungen zum Diencephalon und ihre Regenerationspotenz." In: Pathophysiologia Diencephalica, S. B. CURRI, L. MARTINI, and W. KOVAC (eds.). Vienna, Springer, 1958, p. 53.

519. SPATZ, H., DIEPEN, R., and GAUPP, V. Zur Anatomie des Infundibulum und des Tuber cinereum beim Kaninchen. Zur Frage der Verknüpfung von Hypophyse und Hypothalamus. Dtsch. Ztschr. Nervenheilk. 159:229, 1948.

520. SPIER, N., and KARELITZ, S. The Pickwickian syndrome. J. Dis. Child. 99:822, 1960.

521. SPRAGUE, J. M., LEVITT, M., ROBSON, K., LIN, C. N., STELLAR, E., and CHAMBERS, W. W. A neuroanatomical and behavioral analysis of syndromes resulting from midbrain lemniscal and reticular lesions in the cat. Arch. Ital. Biol. 101:225, 1963.

522. SPURR, J. B., and BARLOW, G. Tissue electrolytes in hyperthermic dogs. J. Appl. Physiol. 28:13, 1970.

523. STARZL, T. E., and MAGOUN, H. W. Organization of the diffuse thalamic projection system. J. Neurophysiol. 14:133, 1951.

524. STARZL, T. E., TAYLOR, C. W., and MAGOUN, H. W. Collateral afferent excitation of reticular formation of brain stem. J. Neurophysiol. 14:479, 1951.

525. STEPHEN, C. R. Fulminant hyperthermia during anesthesia and surgery. J.A.M.A. 202:178, 1967.

526. STEPHENSON, J. N., MELLINGER, R. C., and MANSON, G. Cerebral gigantism. Pediatrics 41:130, 1968.

527. STEVENSON, J. A. F. "Neural Control of Food and Water Uptake." In: The Hypothalamus, W. HAYMAKER, E. ANDERSON and W. J. H. NAUTA (eds.). Springfield, Thomas, 1969, p. 524.

528. STEVKO, R. M., BALSLEY, M., and SEGAR, W. E. Primary polydipsia -- compulsive water drinking. Report of two cases. J. Pediat. 73:845, 1968.

529. STEWART, R. M. On the occurrence of a cerebellar syndrome following heat stroke. Rev. Neurol. Psychiat. 16:78, 1918.

530. STOLL, W. A. Beziehungen des Hypothalamus zur Temperaturregulierung. Helv. Physiol. Pharmacol. Acta 1:C24, 1943.

531. STOTIJN, C. P. J., and NAUTA, W. J. H. Precocious puberty and tumor of the hypothalamus. With report of a case, and a consideration of hypothalamo-hypophyseal connections. J. Nerv. Ment. Dis. 111:207, 1950.

532. STRICKER, E. M., and WOLF, G. Hypovolemic thirst in comparison with thirst induced by hyperosmolarity. Physiol. Behav. 2:33, 1967.

533. STRÖM, G. "Central Nervous Regulation of Body Temperature." In: Handbook of Physiology, J. FIELD, H. W. MAGOUN and V. E. HALL (eds.), sect. 1, vol. II. Washington, D.C., Amer. Physiol. Soc., 1960, p. 1173.

534. STUTINSKY, F. Sur la signification des pituicytes. C. R. Assn. Anat. 41:367, 1954.

535. STUTINSKY, F. S. Recherches expérimentales sur le complexe hypothalamo-neurohypophysaire. Arch. Micr. Morph. Exp. (suppl.) 46:93, 1957.

536. STUTINSKY, F. "Rapports du neurosécrétat hypothalamique avec l'adéno-hypophyse dans des conditions normales et expérimentales." In: Pathophysiologia Diencephalica, S. B. CURRI, L. MARTINI and W. KOVAC (eds.). Vienna, Springer, 1958, p. 78.

537. SUDA, J., KOIZUMI, K., and BROOKS, C. McC. Study of unitary activity in the supraoptic nucleus of the hypothalamus. Jap. J. Physiol. 13:374, 1963.

538. SUNDERMAN, F. W., and HAYMAKER, W. Hypothermia and elevated serum magnesium in a patient with facial hemangioma extending into the hypothalamus. Amer. J. Med. Sci. 213:562, 1947.

539. SWANSON, A. G., and ISERI, O. A. Acute encephalopathy due to water intoxication. New Engl. J. Med. 258:831, 1958.

540. SZENTÁGOTHAI, J., FLERKÓ, B., MESS, B., and HALÁSZ, B. Hypothalamic Control of the Anterior Pituitary. An Experimental-Morphological Study, 3rd ed. Budapest, Akad. Kiadó, 1968.

541. TEITELBAUM, P., and EPSTEIN, A. N. The lateral hypothalamic syndrome. Recovery of feeding and drinking after lateral hypothalamic lesions. Psychol. Rev. 69:74, 1962.

542. THAUER, R. Der nervöse Mechanismus der chemischen Temperaturregulation des Warmblutes. Naturwissensch. 51:73, 1964.

543. THAYSEN, J. H., and SCHWARTZ, I. L. Fatigue of sweat glands. J. Clin. Invest. 34:1719, 1955.

544. THOMPSON, R. H., HAMMEL, H. T., and HARDY, J. D. Calorimetric studies in temperature regulation: The influence of cold, neutral, and warm environments upon pyrogenic fever in normal and hypothalectomized dogs. Fed. Proc. 18:159, 1959.

545. TOKIZANE, T. Hypothalamic control of cortical activity and some observations during different stages of sleep. EEG Clin. Neurophysiol. 17:450, 1964.

546. TÖRÖK, B. Structure of the vascular connections of the hypothalamo-hypophysial region. Acta Anat. 59:84, 1964.

547. TUCCI, J. R., ESPINER, E. A., JAFFER, P. I., LANLER, D. P., and THORN, G. W. Vasopressin in the evaluation of pituitary-adrenal function. Ann. Int. Med. 69:191, 1968.

548. UHTOFF, W. Ophthalmic experiences and considerations on the signs of cerebral tumor and tower skull. (Bowman Lecture.) Trans. Ophth. Soc. U. K. 34:47, 1914.

549. van BOGAERT, L. The thalamic and parkinsonian type of infundibular tumors. The occurrence of glycoregulatory and so-called endocrine disorders. Arch. Neurol. Psychiat. 19:377, 1928.

550. van REETH, P. C., DIERKENS, J., and LUMINER, D. L'hypersexualité dans l'épilepsie et les tumeurs du lobe temporal. Acta Neurol. Psychiat. Belg. 58:194, 1958.

551. VERNEY, E. B. Absorption and excretion of water. The antidiuretic hormone. Lancet 2:739, 1946.

552. VERNEY, E. B. The antidiuretic hormone and the factors which determine its release. Proc. Roy. Soc., B 135:25, 1947.

553. VERTEL, R. M., and KNOCHEL, J. P. Acute renal failure due to heat injury. An analysis of ten cases associated with a high incidence of myoglobinuria. Amer. J. Med. 43:435, 1967.

554. VILLABLANCA, J., and MYERS, R. D. Fever produced by microinjection of typhoid vaccine into hypothalamus of cats. Amer. J. Physiol. 208:703, 1965.

555. von ECONOMO, C. Die Encephalitis lethargica, ihre Nachkrankheiten und ihre Behandlung. Wien, Urban & Schwarzenberg, 1929.

556. von EULER, C. Slow "temperature potentials" in the hypothalamus. J. Cell. Comp. Physiol. 36:333, 1950.

557. von EULER, C., and HOLMGREN, B. The role of hypothalamo-hypophysial connexions in thyroid secretion. J. Physiol. 131:137, 1956.

558. VOTAW, C. L. Certain functional and anatomical relations of the cornu ammonis of the macaque monkey. Anatomical relations. J. Comp. Neurol. 114:283, 1960.

559. WAGNER, H. N., and BRAUNWALD, E. J. The pressor effect of the antidiuretic principle of the posterior pituitary in orthostatic hypotension. J. Clin. Invest. 35:1412, 1956.

560. WALKER, E. A. Murder or epilepsy? J. Nerv. Ment. Dis. 133:430, 1961.

561. WALSH, F. B., and HOYT, W. F. Clinical Neuro-ophthalmology, 3 vol. Baltimore, Williams & Wilkins, 1969.

562. WALTER, W. G., GRIFFITHS, G. M., and NEVIN, S. The electro-encephalogram in the case of pathological sleep due to hypothalamic tumour. Brit. Med. J. 1:107, 1939.

563. WANG, M. B. The distribution and control of osmosensitive cells within the hypothalamus of the opossum (Didelphis virginiana). Neuroendocrinology 4:51, 1969.

564. WASMAN, M., and FLYNN, J. P. Direct attack elicited from hypothalamus. Arch. Neurol. 6:220, 1962.

565. WATTS, J. W., and FULTON, J. F. Intussusception--the relation of the cerebral cortex to intestinal motility in the monkey. New Engl. J. Med. 210:883, 1934.

566. WEIL, A. A. Ictal emotions occurring in temporal lobe dysfunction. A.M.A. Arch. Neurol. 1:101/87, 1959.

567. WEINBERGER, L. M., and GRANT, F. C. Precocious puberty and tumors of the hypothalamus. Report of a case and review of the literature, with a pathophysiologic explanation of the precocious sexual syndrome. Arch. Int. Med. 67:762, 1941.

568. WEIR, J. F., LARSON, E., and ROWNTREE, L. G. Studies in diabetes insipidus, water balance, and water intoxication. Arch. Int. Med. 29:306, 1922.

569. WHEATLEY, M. D. Hypothalamus and affective behavior in cats: Study of effects of experimental lesions, with anatomic correlations. Arch. Neurol. Psychiat. 52:296, 1944.

570. WHERRY, F. E., TRIGG, L. N., GRINDELAND, R. E., and ANDERSON, E. Identification of the hormones secreted by an autonomous mammotropic pituitary tumor in rats. Proc. Soc. Exp. Biol. Med. 110:362, 1962.

571. WHITE, M. G., CARTER, N. W., RECTOR, F. C., and others. Pathophysiology of epidemic St. Louis encephalitis. Ann. Int. Med. 71:691, 1969.

572. WILLIAMS, R. H., and HENRY, C. Nephrogenic diabetes insipidus transmitted by females appearing during infancy in males. Ann. Int. Med. 27:84, 1947.

573. WITTER, H., and TASCHER, R. Hypophysär-hypothalamische Krankheitsbilder nach stumpfem Schädeltrauma. Fortschr. Neurol. Psychiat. 25:523, 1957.

574. WOODS, J. W., BARD, P., and BLEIR, R. Functional capacity of the deafferented hypothalamus: Water balance and responses to osmotic stimuli in decerebrate cat and rat. J. Neurophysiol. 29:751, 1966.

575. YAGI, K., AZUMA, T., and MATSUDA, K. Neurosecretory cell: Capable of conducting impulses in rats. Science 154:778, 1966.

576. YOSS, R. E., and DALY, D. D. Narcolepsy. Med. Clin. N. Amer. 44:953, 1960.

577. XUEREB, G. P., PRICHARD, M. M. L., and DANIEL, P. M. The arterial supply and venous drainage of the human hypophysis cerebri. Quart. J. Exp. Physiol. 39:199, 1954.

578. XUEREB, G. P., PRICHARD, M. M. L., and DANIEL, P. M. The hypophysial portal system of vessels in man. Quart. J. Exp. Physiol. 39:219, 1954.

579. YENERMEN, M. H., BOWERMAN, C. I., and HAYMAKER, W. Colloid cyst of the third ventricle. A clinical study of 54 cases in the light of previous publications. Acta Neuroveg. 17:211, 1958.

580. ZANCHETTI, A. Brain stem mechanisms of sleep. Anesthesiology 28:81, 1967.

581. ZIMMERMAN, H. M. Temperature disturbances and the hypothalamus. A. Res. Nerv. Ment. Dis., Proc. 20:824, 1940.

582. ZONDEK, B., and ASCHHEIM, S. Hypophysenvorderlappen und Ovarium. Beziehungen der endokrinen Drüsen zur Ovarialfunktion. Arch. Gynäkol. 130:1, 1927.

TABLE 27-1. PROPOSED CLASSIFICATION OF DIENCEPHALIC DERIVATIVES[297,298]

Epithalamus (habenular nuclei and stria medullaris thalami)	
Pars dorsalis of thalamus	
Pars ventralis of thalamus	
Subthalamus*	hypothalamus in broader sense
Hypothalamus in narrower sense	hypothalamus in broader sense

*Including subthalamic nucleus, entopeduncular nucleus, and entire globus pallidus.

TABLE 27-2. CLASSIFICATION OF HYPOTHALAMIC REGIONS AND NUCLEI

- Periventricular region
  - Preoptic periventricular nucleus
  - Posterior periventricular nucleus
- Preoptic region
  - Medial preoptic nucleus
  - Lateral preoptic nucleus
- Supraoptic or rostral region
  - Nucleus supraopticus diffusus
  - Suprachiasmatic nucleus
  - Anterior hypothalamic nucleus
  - Supraoptic nucleus
  - Paraventricular nucleus
- Tuberal or middle region
  - Tuberoinfundibular (or infundibular) nucleus
  - Ventromedial nucleus
  - Dorsomedial nucleus
  - Dorsal nucleus
- Posttuberal region
  - Posterior nucleus
- Mamillary region
  - Mamillary body
  - Lateral mamillary nucleus
  - Nucleus intercalatus
  - Premamillary nucleus
  - Supramamillary nucleus
- Lateral region
  - Lateral hypothalamic area
  - Tuberomamillary nucleus
  - Perifornical and intrafornical nuclei
  - Nuclei tuberis laterales

TABLE 27-3. SUBDIVISIONS OF HYPOPHYSIS

Adenohypophysis	Neurohypophysis
Pars infundibularis (pars tuberalis)	Infundibulum (median eminence)
Pars intermedia	Infundibular stem
Pars anterior (pars distalis, anterior lobe)	Infundibular process (pars nervosa, neural lobe)

Other Terms

Pituitary stalk: Infundibulum + pars infundibularis adenohypophyseos + infundibular stem

Posterior lobe: Infundibular process + pars intermedia

Supraopticohypophysial tract: Paraventriculohypophysial + supraopticohypophysial fibers

LEGENDS

Fig. 27-1. Concepts of derivation of diencephalic components. (From Richter.[459]) Heavy black dots: basal plate. Vertical lines: alar plate.

a. The sulcus limitans continues forward in the sulcus of Monro and terminates in the optic recess. Below this sulcus the basal plate is continuous forward as the hypothalamus. Sulcus term., sulcus terminalis. St. Ko. R., Stielkonusrinne (Hochstetter). [Synonyms: sulcus opticus (J. E. Rose), sulcus intra-encephalicus anterior (Kuhlenbeck).]

b. The sulcus limitans terminates in the mamillary recess. The hypothalamus and the other diencephalic components (and the telencephalon) represent derivatives of the alar plate. Gangl. H. Med., medial ganglionic protuberance. Com. plate, commissural plate.

c. The sulcus limitans continues forward in the sulcus of Monro and ends at the foramen of Monro (interventricular foramen). This concept is based on the observation that the basal plate (midbrain tegmentum and subthalamus) undergoes rapid "exhaustion" as compared with the time at which the alar plate (tectum and dorsal thalamus) becomes "exhausted." The ventral thalamus (vertical lines with small dots) is depicted as a transitional area between the subthalamic and dorsal thalamic anlagen. The hypothalamus in the narrower sense (circles) is bounded inferiorly by a floor plate and a lateral floor sulcus.

Fig. 27-2. Human diencephalon A at an early embryonic stage (18 mm.), and B at a later stage (33 mm.). (From Kuhlenbeck; in Christ.[106])

The upper boundary of the hypothalamus is the hypothalamic (or ventral diencephalic) sulcus (hs). An inconstant but frequent posterior extension of lateral infundibular sulcus (ls) divides the hypothalamus into ventral and dorsal parts. The preoptic region (PRE) in the earlier stage is separated from the rest of the hypothalamus by the intra-encephalic sulcus (is), which subsequently becomes the preoptic recess (pr). The entopeduncular nucleus (E) migrates from its hypothalamic anlage (arrow in B) lateralward via the hemispheric stalk to become the internal division of the globus pallidus (P_1). The subthalamic nucleus (SU), a derivative of the dorsal part of the primitive hypothalamus, eventually moves lateralward (arrow in B) to become a component of the subthalamus.

In time the ventral thalamus suffers great reduction coincident with expansion of the dorsal thalamus. Cell masses of the ventral thalamus develop into a thin sheet of cells which covers the inferolateral surface of the thalamus: a medial portion becomes the zona incerta (ZI), which is included as part of the subthalamus, while the lateral portion develops into the reticular nucleus of the thalamus (R). Another portion of the ventral thalamus migrates caudalward to become the pars ventralis both of the lateral geniculate and the medial geniculate body (GV).

The dorsal thalamus (or thalamus) retains its identity throughout ontogenetic development. It is separated from the epithalamus by the dorsal diencephalic sulcus (ds) and from the ventral thalamus by the medial diencephalic sulcus (ms).

A, adenohypophysis; ac, anterior commissure; c, chiasmal ridge; f, interventricular foramen; hn, habenular nuclei; lms, lateral mesencephalic sulcus; M, mamillary body; n, neurohypophysis; pp and pr, pre-

tectal primordium and region; sep, septal region; str, striatum; teg, tegmentum of midbrain. X indicates the uppermost limit of the basal (motor) plate and sulcus limitans of the neural tube.

Fig. 27-3. Derivation of adenohypophysis and neurohypophysis in man. A. From an embryo of about five weeks, showing Rathke's pouch and floor of third ventricle in approximation to each other. B. By the eighth week the neurohypophysis has differentiated and has come into contact with the adenohypophysis. At this stage the adenohypophysis contains a cavity that becomes the residual lumen of Rathke's pouch (L). C. By the eleventh week the hypophysis has assumed the relations characteristic of the adult; the residual lumen (L) of the hypophysis will become the interglandular (or Rathke's) cleft. D. Midsagittal section in the newborn, showing the pharyngeal hypophysis and canal in the region where the stalk of Rathke's pouch was located. (Modified from Arey.[34])

Fig. 27-4. Nuclei of hypothalamus. The nuclei of the medial hypothalamic area, i. e., those situated medial to fornix (F), are the medial preoptic, paraventricular, dorsomedial, ventromedial, posterior, and tuberoinfundibular (or infundibular). The supraoptic nucleus, consisting of three components, lies partly in the medial hypothalamic region and partly in the lateral. Within the more caudal part of lateral hypothalamic area is an accumulation of large and small cells, the tuberomamillary nucleus (in lower drawing). These cells continue medially around the fornix (as the perifornical nucleus) and merge with the cells of the posterior nucleus (in upper drawing). The nuclei tuberis laterales project on to the inferior surface of the hypothalamus. AC, anterior

commissure; HS, hypothalamic sulcus; M, mamillary body; MT, mamillothalamic tract; RN, red nucleus; SG, subcallosal gyrus.

Fig. 27-5. Hypothalamic nuclei, as seen in coronal section at various levels: 1, optic chiasm; 2, infundibulum; 3, postinfundibular region; and 4, mamillary body.

AC, anterior commissure; AL, ansa lenticularis; AMY, amygdala; BP, basis pedunculi; D, dorsal nucleus; DM, dorsomedial nucleus; F, fornix, GP, globus pallidus; HIP, hippocampal formation; IC, internal capsule; IN, nucleus intercalatus; In, infundibulum (median eminence) of neurohypophysis; ITP, inferior thalamic peduncle; LM, lateral mamillary nucleus; LP, lateral preoptic nucleus; M, medial mamillary nucleus (mamillary body); l and m, lateral and medial parts of medial mamillary nucleus; MP, medial preoptic nucleus, MT, mamillothalamic tract; NB, nucleus basalis; OC, optic chiasm; P, paraventricular nucleus; PN, posterior nucleus; PUT, putamen; PV, periventricular region (subependymal cell matrix and overlying ependymal epithelium); SO, supraoptic nucleus; T, thalamus; TI, tuberinfundibular (or infundibular) nucleus; TL, nuclei tuberis laterales; TM, tuberomamillary nucleus; VM, ventromedial nucleus.

Fig. 27-6. Limbic lobe and its major connections with the hypothalamus and midbrain, with emphasis on the origin and destination of the medial forebrain bundle. Concentric areas of archicortex and mesocortex are portrayed in dark and light stipple, respectively. Upper: Afferent pathways to rostral limbic structures. Lower: Efferent pathways from these structures.

AT, anterior thalamic nuclei; CG, central gray of midbrain; DB,

diagonal band of Broca; G, dorsal and ventral tegmental nuclei of Gudden; HAB, habenular nuclei; IP, interpeduncular nucleus; LMA, limbic midbrain area (of Nauta); M, mamillary body; PIT, pituitary gland; SC, superior colliculus; STR MED, stria medullaris thalami. (From MacLean.[364])

Fig. 27-7. Connections of the mesencephalic limbic system (of Nauta) with the hypothalamus and other structures, in the dog. Upper and lower: Afferent and efferent pathways, respectively. Afferent pathways reach the tegmental nuclei of Gudden from the septal region both directly (via the medial forebrain bundle), and indirectly (via the habenular and interpeduncular nuclei). Some of the efferent fibers arising in the dorsal tegmental nucleus and in the periaqueductal gray extend via the dorsal longitudinal fasciculus into the posterior hypothalamic nucleus (P) and the dorsal hypothalamus. Others arising (a) in the tegmental nuclei of Gudden pass via the mamillary peduncle to terminate in hypothalamic structures (mamillary body and medial tuberal region) and the septal region. Still others (b) arising in the ventral tegmental area of Tsai pass into the hypothalamus to reach the more rostral hypothalamus and the septal region. Fibers ending in tuberal nuclei influence, in turn, hypophysial activity. (After Nauta and Kuypers, in Anderson et al.[20])

Fig. 27-8. Some major descending (A and B) and ascending (C) conduction pathways related to the hypothalamus, in the cat. (From Nauta.[400])

A. Medial forebrain bundle, with contributions to it from the hippocampus (Hp), septal region (S), and amygdaloid complex (Am); not included are the olfactory radiations. The medial forebrain bundle extends caudally into the paramedian midbrain tegmental structures,

including the nucleus of Bechterew (NCS) and the nuclei of Gudden (NGd and NGp). Pathways diverging from the paramedian fiber contingent and extending into more lateral tegmental regions are shown as dashed lines.

B. Alternate conduction routes to the paramedian midbrain tegmentum, including those by way of the stria medullaris thalami to the habenula (Hb), and by way of the fasciculus retroflexus to the interpeduncular nucleus (IP), the nuclei of Bechterew and Gudden, and the central gray substance (SGS).

C. Fibers ascending from the paramedian tegmentum into the hypothalamus by way of the dorsal longitudinal fasciculus and the mamillary peduncle.

A, anterior thalamic nucleus; AVT, ventral tegmental area of Tsai; CA, anterior commissure; CI, inferior colliculus; CM, mamillary body; CO, optic chiasm; CS, superior colliculus; DBC, decussation of brachium conjunctivum; HL, lateral hypothalamic area; Hpv, medial and periventricular hypothalamic regions; IL, intralaminar thalamic nucleus; IP, interpeduncular nucleus; P-C, parafascicular-center median nuclei; PL, lateral preoptic area; ST, subthalamic region.

Fig. 27-9. Relationships of the amygdalo-piriform complex to other forebrain structures and to midbrain structures, in Macaca mulatta. (From Nauta.[401])

A. Amygdala (AM), and ventral amygdalofugal projection, components of which are distributed to the substantia innominata (SI), lateral preopticohypothalamic region (PL and HL), nucleus of the diagonal band of Broca (ND), rostral parts of the gyrus fornicatus (IL and AL), olfactory tubercle (synonym: anterior perforated substance) (TO), and medial sub-

division of the dorsomedial thalamic nucleus (DMm). AC, anterior commissure.

B. Projections from the medial subdivision of the dorsomedial thalamic nucleus, mainly to the caudal orbitofrontal cortex (OF) but also extending to other structures, as indicated.

C. Projections from the caudal orbitofrontal cortex (OF). PC, paracentral thalamic nucleus; SP, anterior perforated substance; Teg, subthalamic and rostral mesencephalic reticular substance.

D. Composite of A-C. TI, inferior temporal neocortex. All fiber connections distributed to the lateral preopticohypothalamic region (PL and HL) represent access routes to the medial forebrain bundle.

Fig. 27-10. Arterial circle of Willis, illustrating sources of blood supply of the hypothalamus and pituitary. The branches for the supply of the hypothalamus may be divided into anterior, intermediate, and posterior groups. Arteries passing to the upper neurohypophysis come from the internal carotid, the posterior communicating, and in small measure, from the prechiasmal plexus (the latter not illustrated). The arteries take a circuminfundibular position and give off branches that extend into the infundibular stalk.

Fig. 27-11. Pituitary and adjoining hypothalamus of man. (After J. F. Christ.[103]) The neurohypophysis consists of three parts, the boundaries of which are indicated by interrupted lines: infundibulum, infundibular stem, and infundibular process.

ir, infundibular recess; lt, lamina terminalis; M, mamillary body; OC, optic chiasm; pi em, postinfundibular eminence; pr, preoptic recess; ti, tuberoinfundibular sulcus; 3V, third ventricle.

Fig. 27-12. Blood supply of the pituitary in man. Capillary loops and other capillary formations constitute a first capillary bed, or primary plexus. This extensive capillary system drains through long and short hypophysial portal channels (the hypophysial portal system) into the sinusoids of the adenohypophysis, the second capillary bed. From the adenohypophysial sinusoids, blood is drained by collecting veins (V), which surround the hypophysis. In turn, the blood reaches the intracranial dural venous sinuses, thence the systemic circulation. The first capillary bed is supplied by the superior hypophysial artery (SHA) and inferior hypophysial artery (IHA), the latter arising from the intracavernous part of the internal carotid. The trabecular artery (AT) forms an anastomosis with branches of the inferior hypophysial arteries for the supply of the lower infundibulum; terminals give rise to capillary loops. The vascular supply of the infundibular process is also indicated. L, lateral branch of inferior hypophysial artery. (From Adams, Daniel, and Prichard,[3] and Xuereb, Prichard, and Daniel.[578])

Fig. 27-13. Hypothalamohypophysial neural connections in man. A. The supraopticohypophysial tract (SHT) is indicated as ending in the infundibular process of the neurohypophysis in relation to a capillary vessel in an island of Greving, and the tuberohypophysial tract (THT), as ending in relation to a capillary loop which has emanated from the mantle capillary plexus (MP). B and C are enlargements of the area indicated in A. OC, optic chiasm; PI, pars infundibularis hypophyseos. (C, from J. F. Christ.[103])

Fig. 27-14. Craniopharyngioma. Mid-sagittal view. This cystic tumor fills most of the third ventricle. The white flecks are calcific

deposits, recognizable roentgenographically. The patient was a 19-year-old male. He had had headaches since childhood. Examination in the last year of life disclosed a stiff neck, bilateral papilledema, right hemiparesis, and bilateral Babinski sign. (Armed Forces Institute of Pathology Acc. 138593.)

Fig. 27-15. Tuberal region in a case of pubertas praecox. The patient was a boy aged 33 months. Attached to the tuber cinereum is a relatively large hamartoma in which there are groups of small nerve cells (SC) resembling cells of medial hypothalamus, and scattered large nerve cells (LC) resembling cells of tuberomamillary nucleus (TM). D, dorsal nucleus; DM, dorsomedial nucleus; F, fornix; P, paraventricular nucleus; TI, tuberoinfundibular nucleus; VM, ventromedial nucleus. (From Spatz, Diepen, and Gaupp.[519])

Fig. 27-16. Changes in respiratory rate and in rectal and ear surface temperatures in an unanesthetized goat kept in an environmental temperature of 21°F (-6°C) during the course of three hours while the preoptic "temperature center" of one side was electrically stimulated. The double lining of the respiratory curve (upper curve) indicates duration of panting. Violent shivering (shiv.) appeared at the end of stimulation. The control goat (dashed line) was kept for the same period of time in the cold environment. (From Andersson and Persson.[29])

Fig. 27-17. "Slow d.c. temperature potential" recorded from the rostral part of the hypothalamus (2 mm. dorsal to anterior edge of the chiasm and 0.5 mm. lateral to the median plane) in a cat under urethane anesthesia. A capillary electrode was inserted into this region by the

Horsley-Clarke technic. The brain was warmed by heating the carotid arteries. A change in potential (upper curve) was recorded against another electrode elsewhere in the brain. The rise in hypothalamic temperature (lower curve) was recorded by a thermo-junction. At 38°C the cat panted. Changes in respiration and blood pressure did not influence the potential. (From von Euler.[556])